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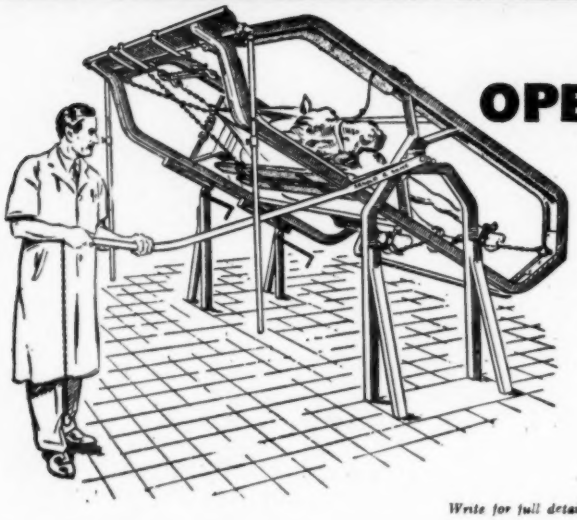

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An Outbreak of Sodium Chloride Poisoning in Turkey Poults

BY

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Veterinary Investigation Centre, Cambridge

SUMMARY.—Two batches of young turkey poults suffered a mortality of 11 and 5 per cent. following the use of a turkey starter meal containing 2.0 per cent. of sodium chloride. The symptoms, post-mortem findings and histopathology are described.

Introduction

IT is well recognised that the presence of an excess of sodium chloride in either the food or drinking water of turkey poults may result in heavy losses characterised by the development of oedema and ascites. The toxicity of sodium chloride for young poults has been shown experimentally by a number of workers (Foss, 1941; James, 1946; Matterson, Scott & Jungherr, 1946; Scrivner, 1946; Bigland, 1950; Bressler, Gordeuk, Callenbach & Pritham, 1951) and a field condition characterised by oedema and ascites, and apparently due to the ingestion of an excess of sodium chloride, or of other sodium salts, has been described in the United States by Scrivner (1946) and in Canada by Bigland (1950). There is a lack of such reports in the British literature, and the following case record may, therefore, be of interest.

Details of Outbreak

This occurred on a Hertfordshire farm where large numbers of day-old poults are purchased each year for rearing and fattening. It affected the first 2 batches bought for the 1955 season, which, at the time of the outbreak, were the only turkeys on the premises. Each batch comprised about 210 day-old Broad Breasted Bronze poults and an equal number of cross-bred bronze poults of the same age.

The first batch was received on April 19th, and was at once put into two wire-floored Motley No. 1 brooders, heated with paraffin oil lamps. The poults were given kibbled grain (equal parts of wheat, barley and maize), insoluble flint grit and unmedicated mains water. A small amount of a proprietary turkey starter meal was offered on the fifth day. A larger amount was given the next day and from the seventh day onwards the meal was offered *ad libitum*, although a feed of kibbled grain was still given at night. The meal was moistened with skimmed milk to give a crumbly consistency. No other additions were made to it, and no green food was given.

Symptoms and Mortality

As will be seen from the Table, no deaths occurred during the first 4 days when the diet consisted solely of kibbled grain. Sporadic deaths commenced on the fifth day, the day on which the meal was first given, reached a maximum on the 10th day and continued till the 18th, when the meal was replaced by kibbled grain. A fresh batch of meal was brought into use a few days later. Subsequent rearing was uneventful, and the farm records showed that the birds reached one month of age without further loss. Forty-eight (11 per cent.) of the 425 poults died during the outbreak.

The second batch, purchased from a different source, and received 7 days later than the first, subsequently showed a very similar history. As before, no losses occurred during the first 4 days when only grain was fed. Losses commenced 3 days after the introduction of the meal, were at their highest 2 days later and continued for 2 days after its withdrawal. Subsequently rearing was uneventful. Twenty (5 per cent.) of the 425 poults died during the outbreak.

Shortly before their death some of the poults were observed sitting in a crouching position, their hocks

TABLE

Days on farm	First batch 425 poults received April 19th — Diet	Number of deaths	Second batch 425 poults received April 26th — Diet	Number of deaths
1	Grain only	Nil	Grain only	Nil
2	"	"	"	"
3	"	"	"	"
4	"	"	"	"
5	Grain + a little meal	2	Grain + a little meal	"
6	Grain + meal	2	Grain + meal	"
7	Grain + meal *ad lib.*	1	Grain + meal *ad lib.*	"
8	"	1	"	2
9	"	1	"	2
10	"	16	"	1
11	"	4	Grain only	[illegible]
12	"	5	"	1
13	"	3	"	2
14	"	3	"	Nil
15	"	5		No further losses up to 1 month of age
16	"	3		
17	"	2		
18	Grain only	Nil		
19	"	"		
		No further losses up to 1 month of age		
Total Losses		48 (11%)		20 (5%)

resting on the wire floor. Gasping respiration occurred in the majority and some birds vomited a watery fluid. About half of the other poults were dull and ruffled. They were very thirsty, and drank about twice the usual amount of water. Many showed loose, whitish droppings. No nervous symptoms were observed.

Laboratory Examination

The examination of a poult from the first batch which had died on the 11th day revealed only an enlarged mottled liver, suggestive of salmonellosis, but cultural investigation produced no evidence of any significant bacterial infection. Four days later 3 more poults from this batch were examined. All 3 showed extensive subcutaneous and pulmonary oedema and marked ascites. One had a dark, mottled liver. Apart from the isolation of *E. coli* from one poult, bacteriological examination gave negative results. Material was selected from these poults for histological examination and a sample of food sent for chemical analysis with reference to the possibility of sodium chloride poisoning. A further 4 poults—two from each batch—were examined on the 17th day. All 4 showed oedematous changes similar to those described above, and in all 4 the liver had a mottled appearance. No evidence of bacterial infection was obtained. Chemical analysis of the meal showed that it contained 2.0 per cent. of sodium chloride. Its content of water soluble salts other than sodium chloride was 0.6 per cent.—a figure which is within the normal range. Both results are expressed as percentages of the meal as received for analysis.

Histopathology

Congestion and oedema were recognised consistently in sections of lung, liver, kidney and heart muscle, stained with haematoxylin and eosin.

The lung tissue showed very marked congestion together with oedema of the alveoli. A large number of erythrocytes and leucocytes, including many eosinophils, were lying free within the alveoli. Some alveoli had collapsed and others showed emphysema.

The sinusoids of the liver were very congested. Some liver cells showed marked fatty changes while others exhibited early necrosis.

The kidney showed acute congestion. There were fatty changes in the tubules, some of which showed necrosis while others exhibited granular changes of the cytoplasm. The lumina contained a pink staining substance and the glomeruli, which were swollen, showed a cellular infiltration. Degenerative changes of the ureter were found. The mucosa showed a catarrhal inflammation and free cells were present in the lumina.

In the myocardium the muscle bundles were separated by oedema, as were some of the individual muscle fibres. The striations tended to be indistinct, and some fibres exhibited a granular appearance. The capillaries were engorged with erythrocytes.

Discussion

The toxic effects of an excess of sodium chloride are not specific to that substance but are associated with the osmotic activity of sodium and its accompanying anion. Scrivner (1946) showed that symptoms and lesions similar to those of sodium chloride poisoning can be produced in young poults by the oral administration of other sodium salts, such as sodium bicarbonate and sodium sulphate.

There is, however, little doubt that the present outbreak was due to the addition of an excess of sodium chloride to an otherwise normal turkey starter ration, giving a total sodium chloride content of 2.0 per cent. The sodium chloride content recommended by Ewing (1947) for rations of this kind is 0.5 per cent.

As mentioned above, the content of water soluble salts other than sodium chloride was 0.6 per cent. This is within normal limits, and suggests that no soluble salts other than sodium chloride had been added to the ration.

The literature reveals a difference of opinion as to whether young turkey poults will tolerate 2.0 per cent. of sodium chloride in the food. Bressler *et al.* (1951) found that the addition of 0.9 per cent. of sodium chloride to a basal turkey starter ration resulted in a considerable mortality from ascites and visceral oedema. The sodium chloride content of the basal ration was not stated, but is unlikely to have exceeded 1.0 per cent. Similarly James (1946) stated that the addition of 1.0 per cent. of sodium chloride to a basal ration of unspecified salt content

resulted in an increased mortality rate, although it was not indicated whether these deaths were characterised by oedema and ascites. Scrivner (1946) found that the addition of 2 per cent. of sodium chloride to a starter mash which already contained 0.5 per cent. resulted in a heavy mortality associated with ascites.

In contrast to these findings, Matterson *et al.* (1946) found that the addition of 2.0 per cent. of sodium chloride was well tolerated by day-old poults provided that the basal ration was relatively salt free. Bigland (1950) failed to produce ascites in day-old poults by the addition of 2.0 per cent. of sodium chloride to a turkey starter ration of unspecified salt content and Atkinson, Boucher and Callenbach (1954) made no mention of ascites or mortality in their report of a similar experiment.

These apparent discrepancies may be associated with differences in the concentration of various sodium salts in the drinking water. Bigland (1950) has shown that this may vary greatly from one farm to another, and it is well established that chicks and poults may suffer toxicity from levels of sodium salts in the drinking water that would be tolerated in the food (Blaxland, 1946; Scrivner, 1946; Kare & Beily, 1948). The toxicity of dietary sodium chloride is also influenced by the potassium intake (Burns, Cravens & Phillips, 1953). Unfortunately no water samples were examined in the present outbreak.

It is of interest to note that a series of similar losses occurred on a nearby farm about 2 weeks before those described above. No laboratory examinations were made, but the circumstantial evidence, including the brand, source and delivery date of the food and the symptoms shown by the poults, suggested that these losses were also due to sodium chloride poisoning.

The system of management on this second farm was very similar to that on the first. The losses occurred in a batch of 104 Broad Breasted Bronze poults which were purchased as "day-olds" and offered the suspect turkey starter meal from the first day. Unmedicated mains water was available *ad libitum*. Sporadic losses commenced on the fifth day and continued until about the 10th or 11th day. Twelve of the 104 poults died during this period. No losses occurred after the 11th day although the same batch of meal was still in use. If this was, in fact, an outbreak of sodium chloride poisoning it is interesting to note that the losses ceased spontaneously when the poults were 10 or 11 days old. The field condition reported by Scrivner (1946) showed a very similar age incidence, and the field outbreaks described by Bigland (1950) also ceased spontaneously. A similar age incidence is seen in the experimental disease in turkey poults and in both the field and experimental disease in chicks. It has been suggested that the susceptibility of newly hatched chicks to sodium chloride poisoning is associated with the incapacity of the kidney to preserve osmotic constancy at this stage of life and with the relatively higher food requirements of young chicks (Paver, Robertson & Wilson, 1953).

As a point of differential diagnosis it is of interest to note that Bullis and van Roekel (1944) reported a similar oedematous condition in young chicks exposed to coal-tar creosote oil, anthracene oil, and mite paints containing these compounds, and that Scrivner (1946) produced oedema and ascites by fumigating day-old poults with formaldehyde.

In the present outbreak the brooders had been cleaned with a 10 per cent. solution of ammonia a week before the poults were received. Formalin had not been used and creosote and other wood preservatives had not been used for at least a year.

Sodium chloride poisoning must also be differential from exudative diathesis. Field outbreaks of this condition have been observed in chicks in New Zealand (Thompson & Smith, 1953) and by the author in Great Britain (unpublished data), but no reports have been found of its occurrence in turkey poults. In the present outbreak the *post-mortem* findings and histology did not support a diagnosis of exudative diathesis.

Acknowledgment.—I wish to thank Mr. C. J. L. Baker, of the National Agricultural Advisory Service, Cambridge, for his examination of the food.

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UNIVERSITY NEWS

Bristol

Professor C. S. G. Grunsell, Professor of Veterinary Medicine, delivered his inaugural lecture, "The Growth of the Discipline of Medicine in Veterinary Science," on Friday, November 29th. He was introduced by the Vice-Chancellor to an audience consisting of his colleagues in the Veterinary School and other departments of the University, students, local practising veterinary surgeons, and members of the public.

In his address, which it is hoped to reprint in a later edition of THE RECORD, Professor Grunsell traced the development of veterinary medicine from its earliest recorded beginning to the present day, with special emphasis on its course in Great Britain. The start of the veterinary schools, the legislation governing the profession, and the significance of the State Veterinary Service were described, followed by an examination of the directions that future investigations might take. In referring to the activities of the Veterinary School in Bristol, Professor Grunsell paid tribute to the pioneer work of the late Professor Blakemore, his predecessor in the Chair of Veterinary Medicine.

Further Experiments on the Epidemiology of Parasitic Bronchitis in Calves

BY
J. F. MICHEL
Ministry of Agriculture Veterinary Laboratory, Weybridge

SUMMARY.—Experiments are described which show that the infection of lungworms acquired by a grazing calf depends on the herbage infestation during a short initial period only if changes in the rate of uptake of larvae from the pasture are continuous. In situations where abrupt changes can occur a calf may suffer disease as a result of infecting larvae which it itself has passed on to the pasture.

A number of important implications of this finding are discussed.

Introduction

IN a recent paper (Michel & Parfitt, 1956), it was shown that the fate of a calf exposed to lungworm infection on an experimental paddock depended on the level of the herbage infestation over the first nine days of exposure. The implications of this finding would seem to be that over a wide range of conditions cattle could not produce on the pasture an infestation dangerous to themselves since they were refractory to reinfection by the time larvae which they had passed became infective and available on the herbage. This was also the conclusion of Michel & Mackenzie (1956) who worked with cattle ranging in age from 6 months to 2 years, under several different conditions of management and in 3 different years.

According to the line of argument that was developed to account for the short "danger period" the calf should not be regarded as entirely immune to reinfection after 9 days of exposure to any rate of uptake of larvae. The rate of uptake of larvae that the calf could withstand at any moment was related to the rate of uptake it had already experienced. In the experimental situation studied the fate of the calf depended on the initial herbage infestation because the level of the herbage infestation at any moment was also related to the level during the preceding period and because the maximum potential rate of acceleration of increase of the herbage infestation was less than the greatest acceleration which the calf could tolerate.

It would follow from these considerations that a calf would not be damaged by a herbage infestation of its own making if changes in the level of herbage infestation are continuous whereas it might be harmed in a situation where abrupt changes in its rate of uptake of larvae were possible. That such situations may occur is suggested by field observations which indicate that some outbreaks in calves are not immediately attributable to exposure to herbage infestations due to larvae passed by other animals and it appeared necessary to investigate further the range of conditions in which the infection produced in the calf did entirely depend on the initial herbage infestation. An experiment was accordingly set up for this purpose.

Methods

Three small paddocks each $\frac{1}{8}$ of an acre in extent were laid out on a moderate Agrostis-rye grass pasture containing little clover. This had not been grazed by cattle for some nine months and could therefore be regarded as clean. The paddocks were separated from each other by double fences 3 feet apart.

The calves used were of the Jersey breed and were reared under conditions calculated to preclude the possibility of accidental infections with lungworms. When put onto the experimental paddocks on the dates indicated in Table I they were 3 months old. Routine precautions against intercurrent parasitic infections consisted of weekly dosing with phenothiazine and fortnightly dusting with DDT powder.

The summer of 1956 was distinguished for its high rainfall and the growth of grass was well maintained throughout the season. Nevertheless it became

TABLE I
DETAILS OF THE ANIMALS USED

Paddock number	Calf number	Date put in paddock	Date removed killed or died		Lungworms recovered *post mortem*					
					> 3 cm.	> 2 cm.	> 1 cm.	> 3 mm.	< 3 mm.	Total
1	253	25.IV.56	5.XII.56	K	—	—	1	4	58	63
	267	1.VI.56	5.XII.56	K	—	—	—	—	37	37
	272	23.VIII.56	3.XI.56	D	1,754	48	204	897	369	3,272
2	237	25.IV.56	30.VI.56	D	109	90	238	1,299	523	2,159
	220	25.IV.56	6.VII.56	D	678	213	320	337	473	2,021
3	245	25.IV.56	29.X.56 5.XII.56	R K	—	—	—	—	1	1
	244	25.IV.56	4.XII.56	R	—	—	—	—	—	—

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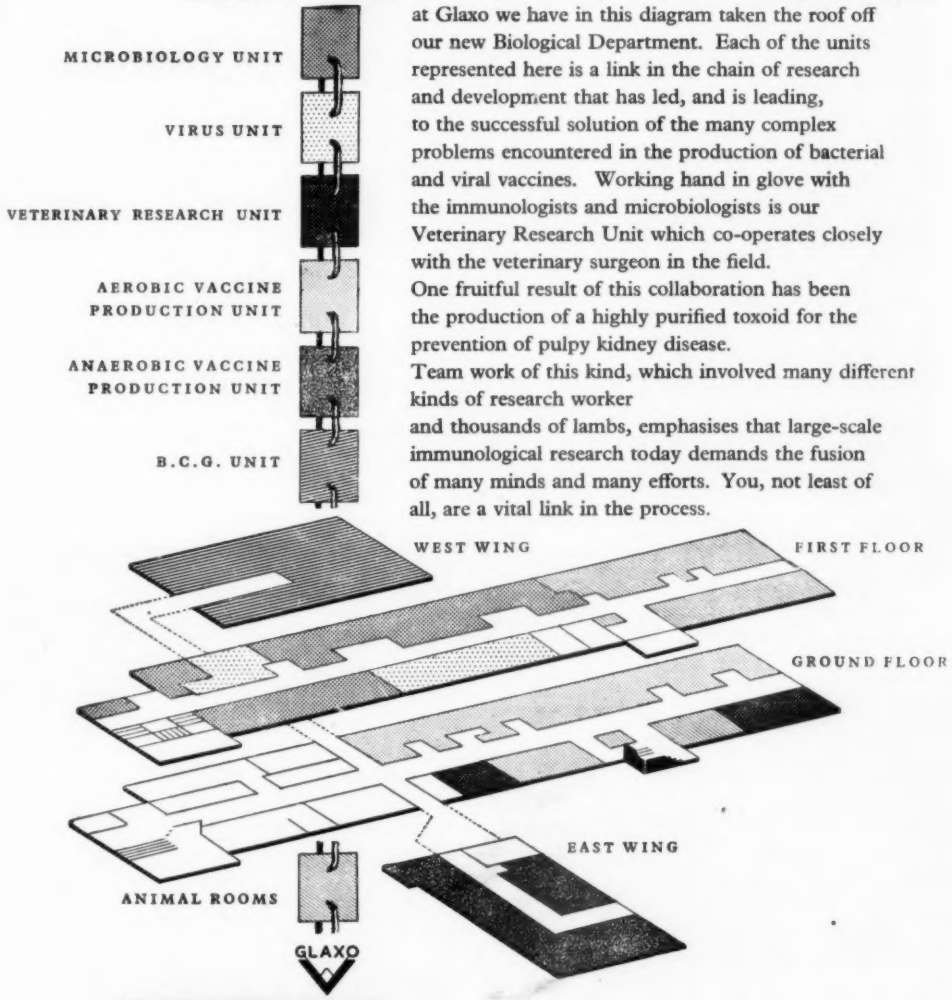

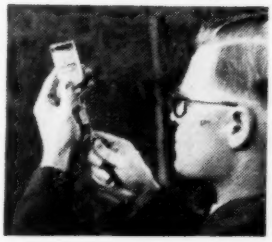

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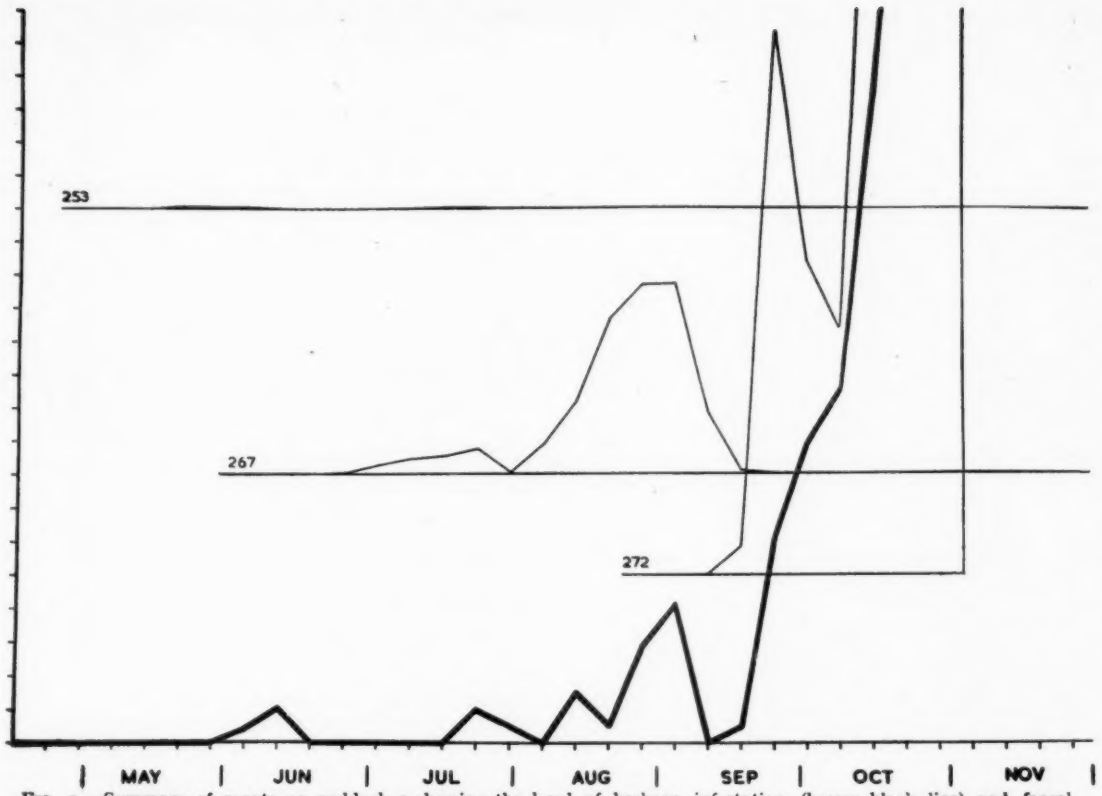

FIG. 1.—Summary of events on paddock 1 showing the level of herbage infestation (heavy black line) and faecal larval counts of the calves. One division on the vertical scale represents one larva per pound of herbage or 25 larvae per gramme of faeces.

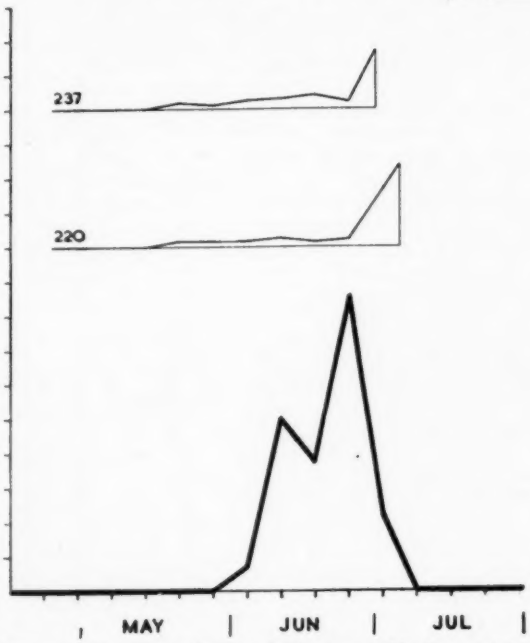

FIG. 2.—The course of the infection on paddock 2 and in the calves grazing on it.

necessary in the middle of August to feed a supplement of kale.

Samples of faeces and of pasture herbage were collected weekly and examined by the procedures described by Michel and Parfitt (1955).

Results and Discussion

The happenings on the three paddocks are shown in figs. 1, 2 and 3 in which are recorded the level of the herbage infestation, expressed as larvae per pound of herbage, and drawn in a heavy black line. Above, in a thinner line, are graphs representing the number of larvae in the faeces of the calves expressed as larvae per gramme of faeces. Details of the animals used are given in Table I.

Paddock 1

A calf, No. 253, was experimentally infected by the oral administration to it of 10 *Dictyocaulus viviparus* larvae on April 25th, 1956. It was put on the paddock on the same day and received a further 30 larvae, 5 days later. This dose of larvae must be regarded as exceedingly small but larvae began to be detected in the faeces of this calf on May 21st. The highest larval count was only 2.1 per gramme of faeces but none the less a herbage infestation rising to 1 larva per pound of herbage resulted. Conditions for the creation of high herbage infestations were evidently excellent.

About this time, on June 1st, a second calf, No.

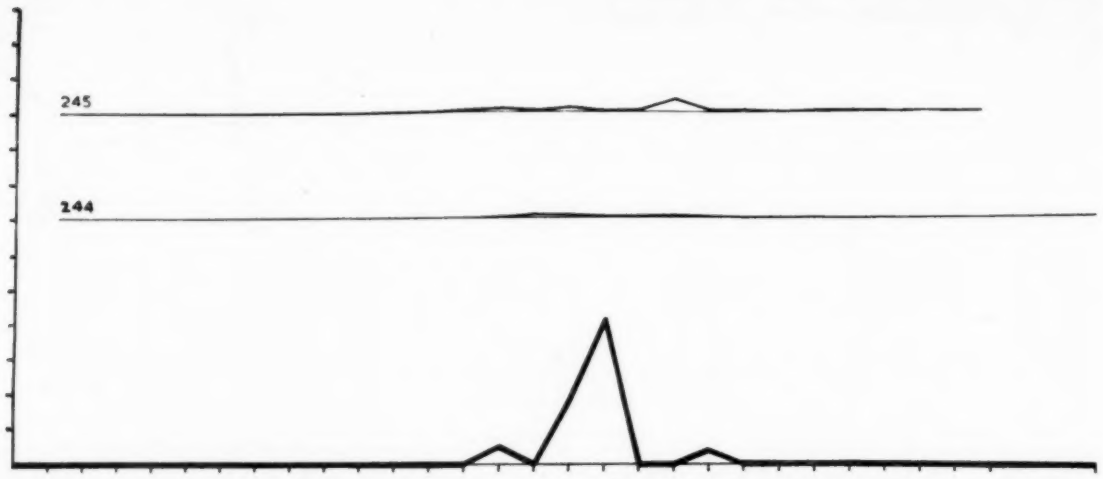

FIG. 3.—The course of the infection on paddock 3 and in the calves grazing on it.

267, was put on the paddock. A moderate larval count resulted in the faeces of this calf rising to a peak of 143 larvae per gramme and the calf showed symptoms of parasitic bronchitis. Climatic conditions continued favourable and the herbage infestation closely reflected the number of larvae being passed.

A third calf, No. 272, was introduced on August 23rd just before the herbage infestation reached its second peak. A very heavy infection resulted in this calf which was reflected both in the faecal larval count and in the number of worms recovered from its lungs when it died.

It is clear that in these conditions where the calves were constantly exposed to infection the infection that each calf acquired depended solely on its uptake of larvae over a short initial period and was in no way affected by subsequent increases in the level of herbage infestation.

Paddock 2

Two calves, Nos. 237 and 220, were each given a dose of 40 *D. viviparus* larvae on April 25th and put onto the paddock. Small numbers of larvae, around 4 per gramme were passed in their faeces but this was sufficient to produce on the herbage, by June 11th, a count of 5 larvae per pound of herbage. The calves which had been picking up no larvae since they were first infected could not withstand this high herbage infestation to which they were suddenly exposed and both succumbed.

In the first calf to die it was found, on *post-mortem* examination, that a fairly high proportion of the worms that it was carrying were immature. In the second calf the proportion of immature worms was smaller, a circumstance suggesting that the worms were still developing.

In the case of this experiment it would seem that the small dose of larvae administered at the start in no way enabled the calves to resist reinfection and they reacted to the lethal herbage infestation which they met in June as though they had not had previous experience of infection. A number of circumstances may have conspired to bring about this result. That highly favourable conditions for "translation" played an important part in permitting lightly infected calves to produce a high herbage infestation is evident, yet the same conditions obtained on the other paddocks where happenings were rather different. That the small size of the initial infection in the calf was not the primary cause would appear from the other paddocks as also from the following experiences with an animal receiving a much larger dose of larvae. A calf received a dose of 2,000 larvae and was put on a clean paddock 2 to 3 acres in extent; its count rose to a peak of 580 larvae per pound and then rapidly fell to zero. The herbage remained negative for larvae until the 6th week and then rose to 7.5 and 13.6 larvae per pound in the following weeks. The calf's faecal larval count began to rise again and in the 11th week it died. At *post-mortem* examination 1,000 worms were recovered, most of which were less than full grown.

It would appear probable that on paddock 2 the failure of the calves to withstand the herbage infestation which they themselves had created was due to the lack of continuity in their uptake of larvae for the uptake that they suffered when larvae began to appear on the herbage was not related to what they had experienced before. This conclusion is amplified by the results of laboratory experiments which show that the degree of "protection" acquired by a calf as a result of receiving a single dose of larvae greater even than the 40 larvae used here is negligible. Experiments which are still in progress with calves receiving small daily doses of larvae suggest that under these conditions a useful measure of protection is acquired rapidly. Similarly in infections of *Trichostrongylus retortaeformis* in rabbits where the protection mechanism is very poorly developed, a single dose of larvae, no matter how great, will not

produce demonstrable resistance to the establishment of worms while repeated doses will.

Paddock 3

On April 25th, 1956, two worm-free calves, Nos. 244 and 245, were put on a clean paddock, the object being to determine whether such a clean system would remain clean even if no particular precautions were taken and to study the consequences if infection were introduced. Until July 16th the system did remain clean, the faeces contained fewer than 1 larva per 10 grammes and the herbage less than 1 larva per two pounds. Starting in June the workers dosing, bleeding or dusting the calves walked first on paddocks 1 and 2 and then came to paddock 3, though to reach paddock 3 from paddock 2 meant walking some 30 yards over another clean piece of grassland. Apparently some infection was introduced into the clean system on paddock 3 in this way. On July 16th very small numbers of larvae were recovered from the faeces of one calf and a week later from both calves and from the herbage. The herbage infestation rose to a level that would have been lethal to a fully susceptible calf but the faecal larval counts of the calves rose no higher and beyond a little coughing they remained unharmed.

In this case though the initial infection was extremely small and conditions for translation excellent, the infection in the calves was unaffected by the herbage infestation which they had created. The conclusion seems inescapable that the difference between the reactions of these two animals to reinfection and those of the two animals on paddock 2 must be due to the manner in which they acquired their initial infection. On paddock 2, calves given a single dose and then withheld from infection were unable to resist reinfection. On paddock 3 the calves which acquired their initial infection over a period and continued to be exposed to infection were resistant to heavy reinfection.

Later in the year the resistance of one of these calves, No. 245, was further challenged. On October 29th, it was transferred to another paddock on which the herbage contained over 20 larvae per pound but it remained unaffected. When it was finally slaughtered on December 5th only one microscopic worm could be found in its lungs.

Conclusions

The results which have been reported would seem to have a very urgent bearing on the management of stock in relation to lungworm infection. Thus it is clear from paddock 1 that it is far safer to put all the year's calves onto a pasture at one and the same time rather than in batches as they reach a certain age at which they are considered strong enough to resist lungworm infection. It is easy enough to visualise how this relatively common practice comes to be perpetuated. The last calves to be put out that is, the youngest, are ultimately the worst affected. What more obvious conclusion, therefore, than that young calves are more vulnerable on account of their youth and it is better not to bring these out of the buildings until later in the season.

A further significant indication emerging from this work is that it is impossible to deduce that a pasture is safe, from the circumstance that susceptible animals have grazed on it without harm. The effect produced on a calf is related in such conditions to the level of herbage infestation when the calves were first put in and if this was low the calves will be unaffected even if they themselves produce on the pasture a dangerous infestation.

It appears also from the results on paddocks 1 and 3 that resistance to reinfection depends on the rate of uptake of larvae which a calf has experienced and not on the size of the infection which it has carried. It is impossible to deduce, therefore, from the severity of symptoms which an animal may have shown, whether or not it is resistant. A calf which has not shown symptoms at any time may yet be refractory to reinfection while it is also possible, though perhaps less likely under normal conditions for a calf which has been clinically affected to be still susceptible.

The most serious implication of this work concerns the very basis of much advice that has been given in the past on the control of parasitic bronchitis. This has been founded on the belief that outbreaks of husk were the outcome of a protracted increase in worm populations on the herbage and in the animal, a small infestation in the calf leading to an increased infestation on the herbage which in turn produced a larger infestation in the calf and so on. The conclusion has been drawn that control must aim at breaking this upward spiral by attempting to withhold cattle, as far as possible, from herbage infestations which they themselves have created. The experiments that have been reported here suggest, however, that an infected animal can only produce herbage infestations dangerous to itself if it is withheld from infection for a time.

On the basis of these results it would seem entirely justifiable to postulate the following situation. A pasture (A) is lightly infected, carrying say 0.2 larvae per pound of herbage. A second pasture (B) is entirely clean. If a calf were put on A and left there one could expect with complete confidence that it would not be harmed by the infection which it would acquire no matter how great a herbage infestation it produced there. If on the other hand the calf were left on A for 2 or 3 days and then transferred to B it could, given favourable climatic conditions, create a herbage infestation which it could not resist. It therefore appears questionable whether the policy of control at present advocated which aims at withholding cattle from herbage infestation of their own making is not attended by grave dangers. Perhaps the only safe course would be to ensure that calves are first exposed to a low level of herbage infestation and then continue to have constant access to that infected herbage.

A great deal more research work will be necessary before methods of management on this new basis can be formulated or recommended.

References

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The Birth of an Indian Rhinoceros Calf at Whipsnade

BY
MARTIN SENIOR
Hon. Veterinary Surgeon to the Zoological Society at Whipsnade Park

THE recent birth of a female rhinoceros at Whipsnade Zoological Park is of great interest and underlines the successful breeding records that are achieved at Whipsnade. It further shows that the experiment embarked upon some 25 years ago by the London Zoological Society in establishing a Zoological Park where the animals could be kept under conditions as nearly corresponding to their natural habitat as possible has proved that this is the ideal method.

There has been only one other birth of an Indian rhinoceros calf in captivity and that was at Basle Zoo in 1956.

Whipsnade received Mohan the male rhinoceros in 1947 and he soon settled down in his paddock and became quite amiable. In 1952 Mohini, a female of about 2 years, was purchased from Assam and came to occupy the stable next to Mohan and they both settled in well but they were not allowed together until Mohini was old enough.

The male, during this interval, reached sexual maturity and occasionally showed signs of " rutting." The female, however, did not reach sexual maturity until 1954 when, on June 8th, the first oestrus period was recorded, lasting for about 24 hours. That day it was decided to allow the 2 rhinos into the paddock together. In view of past experiences at Whipsnade before the war, and those of other Zoos, this was quite a risk, but fortunately all went well. In fact Mohan refused all blandishments of his wife and took refuge in the pool while she, disappointed with him, retired to bed in his stable! This, however, resulted in the two becoming attached to each other, and visitors could often see them lying together in the paddock.

The next oestrus occurred 56 days later on August 3rd, and the oestrus periods of the female continued to recur at an average of 43 days until January 27th, 1955, after which an anoestrus period of 107 days occurred. The next oestrus period was on June 9th, 1955, and 3 periods were observed that summer.

The reactions of the male during these oestrus periods were disappointing as he appeared to take little notice of the female whilst she was in oestrus, but he would show very definite signs of sexual activity 2 days later.

It was then suggested that the diet which consisted of clover hay, green foods in season, and oats with maize, was on too high a nitrogenous plane and that meadow hay should be substituted for clover. It was also known that some varieties of clover appear to contain oestrogenic substance which have a deleterious effect on the sexual activity of some animals.

There was, however, little change in the outward manifestations, although the male did appear to take a little more interest during the oestrus periods of the female, which in all cases lasted approximately 24 hours. After the oestrus period on October 7th, 1955, a second anoestrus period lasting 126 days occurred.

On February 10th, 1956, the female came into season and this was followed by 2 heats at intervals of 39 and 52 days to May 11th. On each occasion the male showed marked sexual activity 48 hours afer each period.

Professor E. C. Amoroso of the Royal Veterinary College was consulted and he suggested that the administration of sex hormones to the male might help. Professor Amoroso was able to obtain supplies of Methyltestosterone that could be given *per os* and the dose having regard to the fact that Mohan weighed nearly 3 tons was computed at 150 mg. t.i.d. for 4 days. This was given in early June and repeated 14 days later. Mohini came into oestrus on June 29th, an interval of 49 days, and the two were heard " whistling " in the paddock at dusk but there appeared little outward change in their usual behaviour.

Professor Amoroso then obtained supplies of Dehydroandrosterone which was administered in early August at the rate of 150 mg. daily for 10 days. The female did not again come into season in 1956 nor in early 1957 when the usual anoestrus period would have been completed. Hopes of a successful mating began to arise and in late September, 1957, the appearance of Mohini began to indicate these hopes were justified. On October 29th a female calf was born after a pregnancy of 16 months.

ABSTRACTS

Salt Tolerance of Turkeys. ROBERTS, R. E. (1957). *Poult. Sci.* **36.** 672-3.

In 3 experiments, turkeys of 8, 26, and 31 weeks of age were given food containing from 0.45 to 8 per cent. of sodium chloride for 3 or 4 weeks. No deaths occurred. Birds receiving 6 or 8 per cent. of salt showed some reduction of weight gain, and the water consumption increased markedly with the salt content of the diet. (*See page* 1115, *" An Outbreak of Sodium Chloride Poisoning in Turkey Poults " by E. A. Gibson.*—Editor.)

The Value of Grit for Chickens and Turkeys. SCOTT, M. L., and HEUSER, G. F. (1957). *Poult. Sci.* **36.** 276-83.

The authors state that a supply of insoluble grit is necessary for the maximum growth, efficiency, and production of chickens, growing turkeys, and laying hens whose diet consists of mash and grain. In each case the birds preferred feldspar grit to granite grit.

Limestone grit and oyster shell were not suited to the dual purpose of supplying additional calcium and aiding the grinding action of the gizzard. A supply of limestone grit apparently helped to prevent the occurrence of enlarged hock disorder in growing turkeys, but the reason for this action was obscure.

E. A. G.

Siamese Twin Piglets

We are indebted to Dr. W. M. McKay, of Cyanamid of Great Britain Ltd., for the accompanying text and photographs.

In THE RECORD of September 24th, 1955, the writer published a description of Siamese twins in pigs, and as a result of this, Mr. R. S. Cowie, M.R.C.V.S., of Keith, Banffshire, sent particulars of thoracophagus Siamese twins in pigs and obtained photographs of the monster. As will be seen from the accompanying photographs the anatomical position of the two pigs is self explanatory. It is understood that there were two hearts, but the liver was common to both pigs. The two pigs were full time and survived 5 to 6 hours after birth.

The photographs give a good idea of the abnormalities present.

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The Animal Health Trust Farm Livestock Research Station

THE latest addition to the activities of the Animal Health Trust, founded in 1942, is the Farm Livestock Research Station which was opened officially by H.R.H. Prince Philip on December 6th.

Situated in the village of Stock, some 5 miles from Chelmsford, Essex, the new laboratories stand in some 60 acres of pleasantly wooded park and pasture land adjacent to Lilystone Hall. It was in 1955, through the generosity of the Trustees of the Boreham Institute, Essex (then under the chairmanship of the late Lord Perry), that the Animal Health Trust received the offer of these new premises. The Boreham Trust undertook to erect at their own expense on land surrounding Lilystone Hall—the home of the late Lord Perry—the necessary laboratories and other scientific buildings required by a research establishment and to lease the whole property to the Animal Health Trust at a " peppercorn " rental. This offer was gratefully accepted and the foundation stone of the new station was laid by the Duke of Norfolk on March 1st, 1956.

The modern buildings standing on their own site of some 16 acres comprise at present a main building containing 10 laboratories, administrative offices, photographic dark room, media and preparation rooms, and stores; a large-animal house with loose-box accommodation and food store; housing for smaller stock; a piggery; and post-mortem room. Lilystone Hall itself with its magnificent formal garden is available to the Trust for offices, conference and lecture rooms, and flats for some of the laboratory personnel.

The Director of this new station is Dr. K. C. Sellers, PH.D., M.R.C.V.S., D.V.S.M., and members of his staff include Dr. H. Williams-Smith, D.SC., B.SC., PH.D., F.R.C.V.S., DIP.BACT.(LOND.)—an outstanding authority on bacteriology; Mr. A. L. Ogden, B.LITT., M.R.C.V.S., D.V.S.M., specialising at present in bovine infertility; Mr. G. C. Ashton, B.SC., in charge of the biochemistry department; Mr. G. Skulski, M.R.C.V.S., pathologist; and Mr. W. E. Crabb, A.I.M.L.T., chief technician, who has been associated with Dr. Williams-Smith in much of his research work.

The most important achievements of the Station to date have been bacteriological research in which work commenced under the guidance of the late Dr. Minett at Houghton Grange has been carried on by Dr. Williams-Smith. His research into the bacterial causes of scour in young animals, with particular reference to the production of resistant strains of *Bact. coli* in young stock receiving antibiotic-supplemented food has been widely publicised in scientific journals. Dr. Smith's discovery of a 6-hour sensitivity test to antibiotics, which is carried out on rectal swabs from young stock affected with scours, now enables the correct antibiotic treatment to be commenced at once and is of great value to the practising veterinary surgeon and farmer alike. It is hoped in the future to extend this work to include studies of managemental and environmental causes of scour.

Mr. A. L. Ogden started his survey of losses in dairy cattle whilst an Animal Health Trust Scholar at Oxford, and since infertility was found to be of major economic importance it was decided to continue his work along this line. Based on Stock, he is carrying out an intensive survey on reproductive wastage in dairy herds in East Anglia. This work is being done in full co-operation with the Milk Marketing Board Cattle Breeding Centre and will take some 3 years to complete. It is hoped to publish an interim report in about 6 months.

In the biochemistry department, Mr. G. C. Ashton is studying the serum-protein pattern of cattle by a technique known as starch gel electrophoresis. Five types of " serum-protein pattern " have so far been distinguished—the types varying from breed to breed. These " serum-protein patterns " are inherited and an intensive study is being carried out on herds throughout the country to determine whether there is a connexion between " serum-protein patterns " and desirable qualities in dairy cattle such as high butter fat content of the milk.

This work has already revealed a possible " lethal factor " and this particular point is being further investigated. Such " serum patterns " will serve as an additional test in distinguishing between monozygous and dizygous twins.

Work in the pathology department has been curtailed due to the illness of Mr. Skulski but it is hoped that he will be out of hospital shortly and able to resume his work.

As well as this research at present in hand, much work has been done on Johne's disease, ringworm, and losses in breeding ewes, and as facilities at the Station increase investigations are to be carried out into vitamin A and iodine metabolism, pulpy kidney disease, Johne's disease, and the possibility of milk infection. It is also hoped to intensify the study of the causes of scour and the production of resistant strains of bacteria. A small sheep flock is already kept and a pig unit is to be built up in the near future.

The station also offers a consultative and diagnostic service and already over 1,800 specimens have been dealt with. Such a service as this is of inestimable value to practising veterinary surgeons who are working in co-operation with the Station.

Such an enterprise as this is not without heavy expense. It has been estimated that the running costs will be in the order of £40,000 a year for the next few years rising to £100,000 a year when the Station is fully developed. Though such sums are considerable they are small in comparison to the oft-quoted figure of £80,000,000 annual loss from animal disease.

Dr. W. R. Wooldridge, the Scientific Director of the Animal Health Trust, must be justly proud of this new research station and he deserves the best wishes of all in this, his latest venture.

ROGER MASSEY.

News and Comment

THE THOMAS BAXTER PRIZE FOR 1957

On Wednesday, November 27th, Dr. A. W. Stableforth, M.R.C.V.S., D.V.S.M., was presented with the Thomas Baxter Prize for 1957 by the Minister of Agriculture, Mr. Heathcoat Amory. The presentation was made at a luncheon held at the Café Royal. Sir Richard Haddon presided, and among those present were Dr. W. R. Wooldridge, representing the B.V.A., the President of the R.C.V.S., Mr. G. N. Gould, and the Registrar, Mr. W. G. R. Oates, the Chief Veterinary Officer, Mr. J. N. Ritchie, and, from the Ministry of Agriculture, Sir Richard Manktelow and Mr. C. P. Quick.

The Thomas Baxter Prize is given yearly to mark outstanding service in the field of milk production, and this year's prize was for work towards improving the health of dairy cattle. It has been awarded to Dr. Stableforth chiefly in recognition of his important work on contagious mastitis and brucellosis, although his work on tuberculosis and other diseases was also remembered.

Dr. Stableforth was born in Devon in 1902, and qualified M.R.C.V.S. in 1923. After qualifying he joined the staff of the Research Institute in Animal Pathology of the Royal Veterinary College, and began his work on the problems of contagious mastitis and brucellosis. His first paper on mastitis, written in conjunction with F. C. Minett and S. J. Edwards, was published in 1929.

In 1939 he was appointed Head of the Department of Bacteriology at the Veterinary Research Laboratories of the Ministry of Agriculture, Weybridge. He became Deputy Director of the Laboratories in 1948, and two years later was appointed Director both of the Central Veterinary Laboratories and the Veterinary Investigation Service of the Ministry of Agriculture.

He was the first veterinary surgeon in Britain to make use of sulphonamides against contagious mastitis, and he and his co-workers were the first to use penicillin against the disease on a large scale. They also played a vital part in the development and application of the S19 vaccine against brucellosis.

Dr. Stableforth has taken a leading part in many studies organised by the F.A.O., the World Health Organisation, and the Agricultural Research Council.

This is the eighth annual award of the Thomas Baxter Prize. It is administered by a Committee of leading farmers and scientists, and carries the Thomas Baxter Trophy, a gold medal and £100. Dr. Stableforth was awarded the John Henry Steel Memorial medal last year, and the profession will receive the news of this new award with great satisfaction.

AMERICAN PUBLIC HEALTH ASSOCIATION'S 85th ANNUAL CONFERENCE

The 85th Annual Conference held at Cleveland, Ohio, November 11th to 15th, 1957, was attended by 4,250 delegates from all parts of the United States as well as from a number of overseas countries.

At the first General Session, before a crowded audience in the vast auditorium in Cleveland, speeches were made by selected representatives of participating countries. The first speech was delivered by Professor Harold Burrow of the Royal Veterinary College, London, on behalf of Great Britain; this was followed by those on behalf of Russia, Norway, and other overseas countries. Professor Burrow spoke on the close and friendly relations existing between public health workers in U.S.A. and Great Britain and of the benefits to mankind that could result from a pooling of the knowledge possessed by these two English-speaking nations. He paid tribute to the work of the late Dr. Reginald Atwater, formerly Secretary of the American Public Health Association, whose recent untimely death was mourned in Great Britain as much as in the United States.

The conference of public health veterinarians held its first meeting on the following day, when Professor Burrow spoke on "Veterinary Public Health in the United Kingdom." On the same evening, Professor and Mrs. Burrow were the guests of honour at the annual dinner of the public health veterinarians. Later in the week, before the laboratory section of the conference, Professor Burrow spoke on "Milk and Dairy Hygiene in Great Britain."

At the second General Session the presentation took place of the 1957 Albert Lasker Awards for research and distinguished service in the field of public health. Among the recipients was Dr. R. E. Shope, well known to the veterinary profession for his work in the field of veterinary virology.

The presence for the first time in the history of the American Public Health Association of a veterinary surgeon representing British public health at this conference gave much pleasure to veterinarians in the United States.

ELECTION OF MEMBERS OF THE R.C.V.S. COUNCIL

The following Statutory Notice is published at the request of the Royal College:—

In accordance with the provisions of the Veterinary Surgeons Act, 1948, five members of the said Council, who must be members of the Royal College, will be elected in 1958 by members of the Royal College residing outside the Republic of Ireland.

Five present members of Council will retire at the Annual General Meeting in 1958 and are eligible for re-election, namely:—

A. J. Wright, Esq.
Professor C. Formston.
J. F. D. Tutt, Esq.
Miss J. O. Joshua.
H. Holroyd, Esq.

Nominations of persons for election to the Council must be submitted in writing on a form which may be obtained from the undersigned, and which must be returned to him duly completed before January 31st, 1958.

Each such nomination form must bear the signature of the proposer and seconder, who must not be present members of Council, and must be countersigned by the nominee.

W. G. R. OATES,
Registrar.

Veterinary Surgeons Acts, 1881-1948

9, Red Lion Square,
London, W.C.1.

IN PARLIAMENT

Foot-and-Mouth Disease

LIEUT.-COMMANDER MAYDON (November 25th): My right hon. Friend is no doubt aware of the deep anxiety felt in farming circles about the possibility of the foot-and-mouth disease virus being imported in chilled or frozen meat. Can he say whether experiments have been going on to see whether there are any methods of killing this virus when it comes in in imported meat?

MR. AMORY: I share the anxiety to which my hon. and gallant Friend refers.

MR. HURD asked the Minister of Agriculture, Fisheries and Food if his veterinary officers have been able to trace the source of the infection which made it necessary for him to declare the counties of Berkshire, Dorset, Hampshire, the Isle of Wight, and Wiltshire, a controlled area last week; if the movements of all contact animals have now been traced; and when he expects to free this area from control.

MR. AMORY: No definite conclusion has yet been reached as to the probable cause of the outbreak of foot-and-mouth disease in Hampshire last Monday. All the relevant movements, which numbered more than 2,500 from five markets, were traced by Thursday, November 21st. I hope to be able to remove the controlled area restrictions as from midnight tonight. I should like to take this opportunity to thank farmers, auctioneers, local and market authorities, and the police, who have rendered invaluable help.

MR. HURD: Will my right hon. Friend take the opportunity afforded by the presence in this country of the Argentine Minister of Agriculture to discuss with him ways and means by which we, who perhaps lead in research into foot-and-mouth disease, can help the Argentine to develop an effective safeguard by way of vaccination so that animals coming here in the form of frozen and chilled meat are in fact vaccinated and made harmless for carrying disease before they are shipped?

MR. AMORY: I am hoping to meet the Argentine Minister of Agriculture this week, and this is a question which I hope to have an opportunity of discussing.

R.C.V.S. OBITUARY

We record with regret the death of the following member of the profession:—

GARRY, Ernest Walter, M.C., 8, St. Martin's Square, Chichester, Sussex. Graduated July 13th, 1922, at the Royal Veterinary College, London. Died November 25th, 1957.

VISIT BY R.C.V.S. PRESIDENT TO BRITISH CARIBBEAN CONVENTION

Mr. G. N. Gould, President of the Royal College of Veterinary Surgeons, has accepted an invitation to be a principal speaker at the British Caribbean Convention, to be held in Trinidad from May 24th to 31st, 1958.

Besides giving papers and clinical demonstrations to the Convention and in other West Indian islands, he will take part in broadcast discussions. His tour is under the auspices of the British Council and he will probably also visit Jamaica, Barbados, British Guiana, and Latin-American countries both to lecture and discuss veterinary problems with Government authorities.

COMING EVENTS

December

11th (Wed.). Ordinary General Meeting of the Sussex Veterinary Society at the Old Ship Hotel, Brighton, 2.30 p.m.

Annual General Meeting of the North Wales Division at the Gwydyr Hotel, Bettws-y-Coed, 2 p.m.

General Meeting of the Midland Counties Veterinary Association at the Swan Hotel, Stafford, 2.45 p.m.

Annual General Meeting of the Scottish Branch at the Royal (Dick) School of Veterinary Studies, Edinburgh, 2.15 p.m.

Meeting of the South-East Midlands Veterinary Medical Association at Franklin's Gardens Hotel, Northampton, 7.30 p.m.

12th (Thurs.). Meeting of the East Midlands Division at the University School of Agriculture, Sutton Bonington, 2.30 p.m.

13th (Fri.). General Meeting of the North of England Veterinary Medical Association in the Agricultural Section Room, King's College, Newcastle upon Tyne, 2.30 p.m.

19th (Thurs.). Annual Dance of the V.V.B.F. Ladies' Guild, Dumfries and Galloway Division, in the Cairndale Hotel, Dumfries, 8.30 p.m.

Ordinary General Meeting of the South-Eastern Veterinary Association at the Royal Star Hotel, Maidstone, 2.30 p.m.

20th (Fri.). 9th Annual General Meeting of the A.V.T. & R.W.'s. Southern Region at the Royal Veterinary College, Camden Town, N.W.1, 12 noon.

January

8th, 9th and 10th (Wed., Thurs. and Fri.). R.C.V.S. Committee and Council Meetings.

22nd, 23rd and 24th (Wed., Thurs. and Fri.). B.V.A. Committee and Council Meetings in London.

FOOT-AND-MOUTH DISEASE

The areas described in the schedules below are declared to be Infected Areas for the purpose of preventing the spread of foot-and-mouth disease:—

The County Boroughs of Bolton, Bury and Wigan.

IN THE COUNTY OF LANCASTER

The Boroughs of Darwen, Chorley, Leigh, Eccles, Farnworth, Radcliffe, Prestwich and Swinton and Pendlebury.

The Petty Sessional Divisions of Bolton, Darwen and Leigh.

In the Petty Sessional Division of Leyland Hundred: The parishes of Withnell, Wheelton, Heapey, Whittle-le-Woods, Euxton, Charnock Richard, Heath Charnock, Heskin, Coppull, Adlington and Anderton.

In the Petty Sessional Division of Wigan: The parishes of Wrightington, Worthington, Shevington, Standish-with-Langtree, Haigh, Aspull, Orrell, Ince-in-Makerfield, Hindley, Billinge-and-Winstanley, Ashton-in-Makerfield, Abram and so much of the parish of Up Holland as lies to the east of the road running from Appley Bridge *via* Bank Top, Hall Green and Up Holland Station to King's Moss including the said road.

In the Petty Sessional Division of Warrington: The parishes of Haydock, Newton-le-Willows, Winwick, Croft and so much of the parish of Golborne as lies within the Petty Sessional Division.

In the Petty Sessional Division of Manchester: The parishes of Worsley and Irlam.

In the Petty Sessional Division of Bury: The parishes of Tottington, Whitefield and so much of the parish of Ramsbottom as lies to the west of the main road (A56) running from Rawtenstall to Bury including the said road.

In the Petty Sessional Division of Blackburn: The parishes of Livesey, and Yate and Pickup Bank.

IN THE COUNTY OF WILTS

In the Petty Sessional Division of Tisbury and Mere: The parishes of Stourton with Gasper, Zeals, Mere, Sedgehill, West Knoyle and Kilmington and so much of the parish of East Knoyle as lies to the west of the main road (A350) running from Shaftesbury *via* East Knoyle to Warminster, including the said road.

In the Petty Sessional Division of Warminster: The parishes of Maiden Bradley with Yarnfield and Kingston Deveriil.

IN THE COUNTY OF DORSET

In the Petty Sessional Division of Shaftesbury: The parishes of Buckhorn Weston, Gillingham, Silton and Bourton.

IN THE COUNTY OF SOMERSET

In the Petty Sessional Division of Wincanton: The parishes of Cucklington, Stoke Trister and Penselwood, so much of the parish of Charlton Musgrove as lies to the east of the road (B3081) running from Wincanton to Bruton, excluding the said road, and so much of the parish of Brewham as lies to the east of the railway running from Bruton to Westbury, excluding the said railway.

In the Petty Sessional Division of Frome: So much of the parish of Witham Friary as lies to the east of the railway running from Bruton to Westbury, excluding the said railway.

ADDRESSES OF DISEASE INFECTED PREMISES

The list given below indicates, first the county in which are situated the premises on which disease has been confirmed, followed by the postal address and date of outbreak.

Anthrax

Ches. Home Farm, Adlington, Macclesfield (Nov. 28).

Derbys. Marston Common Farm, Marston Montgomery (Nov. 25).

Wigtown. California Farm, Wigtown (Nov. 26).

Yorks. Carr House, Kirkby Mazzeard, Ripon (Nov. 25).

Fowl Pest

Lancs. Thompsons Farm, Tanner Smith Lane, Mawdsley, Ormskirk; Sundial, Highfield Road, Croston, Preston (Nov. 25); 513, Leyland Lane, Leyland; Stainfield, Gill Lane, Longton, Preston; Worsley Farm, Back Lane, Charnock Richard, Chorley; Saltpit Farm, Mawdsley, Ormskirk; Pear Tree Farm, Forton, Preston; Holms House Farm, Leyland, Preston; Broadfield House, Dawbers Lane, Euxton, Chorley; 626, Leyland Lane, Leyland, Preston; School Farm, Lane Head, Gt. Eccleston, Preston; Little Moss Farm, Longmeany Gate, Leyland, Preston (Nov. 26); Benizes Farm, Ulnes Walton, Preston; 257/69, Ridley Lane, Mawdsley, Ormskirk; City Farm, Mawdsley, Ormskirk; New Lane Poultry Farm, Eccleston, Chorley (Nov. 27); 6, Woodcock Estate, Lostock Hall, Preston; Farrers Farm, Grange Lane, Hutton, Preston; Saw Mill Cottage, Southport Road, Ulnes Walton, Preston; Kelmadene, Southport Road, Ulnes Walton, Preston; Marshlands, Shirley Lane, Longton, Preston (Nov. 28); Broadfield Nurseries, Cow Lane, Leyland, Preston; Marl Hey, Lydiate Lane, Eccleston, Chorley; Culbeck House Farm, Dawbers Lane, Euxton, Chorley; Shire Farm, Oldfield, Carr Lane, Hardhorn, Blackpool (Nov. 28); Nook Farm, Bretherton, Preston; Tan House Farm, Charnock Richard, Chorley (Nov. 29); The Croft, Forton, Preston; Bluestone Farm, Mawdsley, Ormskirk; Hilton Hall Farm, Eccleston, Chorley (Nov. 30); Jumps Farm, Bretherton, Preston (Dec. 1).

Norfolk. Grundle Farm, Wattisfield, Diss (Nov. 25); Clay Lane, Hepworth, Diss (Nov. 30).

Swine Fever

Berks. Plot 21, Goddard Farm Allotments, Basingstoke Road, Reading (Nov. 25).

Dorset. Allotments, Filbridge, Sturminster Newton; Manor House Farm, Ibberton, Blandford Forum (Nov. 25); Yarde Farm, Pimperne, Blandford Forum (Nov. 29).

Herts. Bells Hill Allotments, Barnet (Nov. 29).

Kent. South Park Farm, Penshurst, Tonbridge (Nov. 26); Westbrook Farm, Cudham, Sevenoaks (Nov. 28).

Leics. The Piggeries, Enderby Road, Thurlaston (Nov. 25).

Middx. 3, Horton Road, Stanwell Moor, Staines (Nov. 25).

Norfolk. Dell Farm, Ingham, Norwich (Nov. 25); The Ashes Farm, Carleton Rode, Norwich; The Limes Farm, Tibenham, Norwich; Low Farm, Drayton, Norwich (Nov. 29).

Notts. Bassingfield Lane, Bassingfield, Radcliffe-on-Trent; Smallholding, Mill Lane, Willoughby-on-the-Wolds (Nov. 25); Lascelles Avenue, Gedling (Nov. 27).

Surrey. Fair Acres Farm, 26, Yew Tree Way, Addington, Croydon (Nov. 27).

Sussex. Blackmores Farm, Wivelsfield, Haywards Heath (Nov. 26).

Wilts. South Down Farm, Coombe Bissett, Salisbury (Nov. 25).

Worcs. 40, High Street, Bromsgrove (Nov. 29).

Yorks. Slack Lane Piggeries, Crofton, Wakefield (Nov. 29).

CORRESPONDENCE

The views expressed in letters addressed to the Editor represent the personal opinions of the writer only and their publication does not imply endorsement by the B.V.A.

Public Relations and the Press

Sir,—Mr. Harold Smith's letter (*Vet. Rec.* **69**, 1,078) emphasises in the last paragraphs a state of affairs which has often caused me to contemplate a letter to the lay press, but for reasons of lack of time or for fear of transgressing professional ethics, private practitioners hesitate to enter into newspaper correspondence.

Recently there has been correspondence in *The Daily Telegraph* on the subject of dogs and cats in

quarantine. Some of the letters made statements which were untrue regarding the laws of quarantine and the nature of rabies infection. Most correspondents gave shocking accounts of dogs kept in filthy conditions—starving, ill, and so on—which is a reflection on our profession because all quarantine premises are under the direct care and supervision of veterinary surgeons. I fully expected to see some authoritative statement refuting these charges by a member of the profession or the Ministry of Agriculture—but only more and more scurrilous letters appeared so I eventually wrote a letter myself stating the true facts. Needless to say my letter was not published.

Perhaps if someone of more importance than myself had written, the true facts could have been presented to the public, most of whom are now convinced, owing to the one-sided nature of the correspondence, that quarantine regulations are obsolete and that the veterinary surgeons in charge are neglectful, if not actually cruel.

Yours faithfully,
LUCY R. ROBINSON.

1, King George's Place,
Maldon,
Essex.

November 25th, 1957.

New Veterinary Organisations

Sir,—I am sorry that there was some ambiguity in my letter in your issue of November 16th. However, the fact that the B.S.A.V.A. is a separate organisation from the B.V.A. does not alter the grounds on which I criticised its activities. Mr. Brian Singleton states in his letter in your issue of November 23rd that several members of the B.S.A.V.A. executive committee also serve on the B.V.A. Council, and that one of their first actions in their new capacity was to approve the appointment of regional Public Relations Officers. Why could they not have pressed for these appointments to have been made within the framework of the B.V.A.? Then these P.R.O.'s would indeed represent the great majority of veterinary surgeons and not some 300 of them only.

I am somewhat staggered by Mr. Singleton's views on the relationship between neighbouring practitioners. He must have been singularly unfortunate to have encountered misunderstanding and suspicion from his neighbours. I have not so far found it necessary to attend meetings in order to be on good terms with my fellows, though I certainly enjoy their company. Why should a new publication be necessary to circulate abstracts from world veterinary literature and current research work? Are not these items always welcome in THE RECORD which is read by the great majority of members?

I have no desire to criticise the efforts of those who wish to raise the status of the profession, but I do not feel that a further splitting of our small numbers is the way in which this should be done. Unity is strength and if the profession is to command the respect to which it is undoubtedly entitled then its members must speak with one voice.

Yours faithfully,
HAROLD L. SMITH.

Manor House,
Rowde,
Devizes.

November 23rd, 1957.

Foot-rot in Sheep

Sir,—May I draw the attention of those of your readers who are interested in the treatment and control of ovine foot-rot to a most interesting and instructive article in the October, 1957, issue of the *Australian Veterinary Journal*? The author of this paper, whilst presenting an admirable and unbiased comparison of the efficacy of an ever-increasing number of so-called remedies for foot-rot, emphasises, in a brief review of the rate of relapse following the administration of these various forms of treatment, that " in an endeavour to reduce the cost of treatment, cheapness has replaced efficacy."

Significantly, so great is the importance apparently placed by Australian workers with regard to the depredations of the foot-rot organism, both in the individually affected animal and *en masse*, that one speaker during the ensuing discussion considered " that results with a highly efficient drug might more than compensate for high cost," whilst another speaker maintained that " the financial gains from the recovered sheep far outweighed this cost."

Incidentally, Mr. A. Huet Owen's contention (*Vet. Rec.* **69.** 1114) that " the use of an ointment instead of a tincture presents certain advantages " does not apparently bear comparison with the author's findings, where it is stated that " a similar delay in relapse into obvious foot-rot was observed by Thomas (*loc. cit.*) with terramycin as an alcoholic solution or an ointment. On the other hand, there is no evidence that delayed relapses occur with 10 per cent. Chloromycetin."

From this survey, therefore, it would appear that the application of chloramphenicol* " remains the obvious choice of reliable substances capable of effecting complete cure with few treatments . . ."

Yours faithfully,
R. JONES PUGH,
Head of Veterinary Department.

Parke, Davis & Company, Limited,
Staines Road,
Hounslow,
Middlesex.

December 2nd, 1957.

* Chloromycetin.

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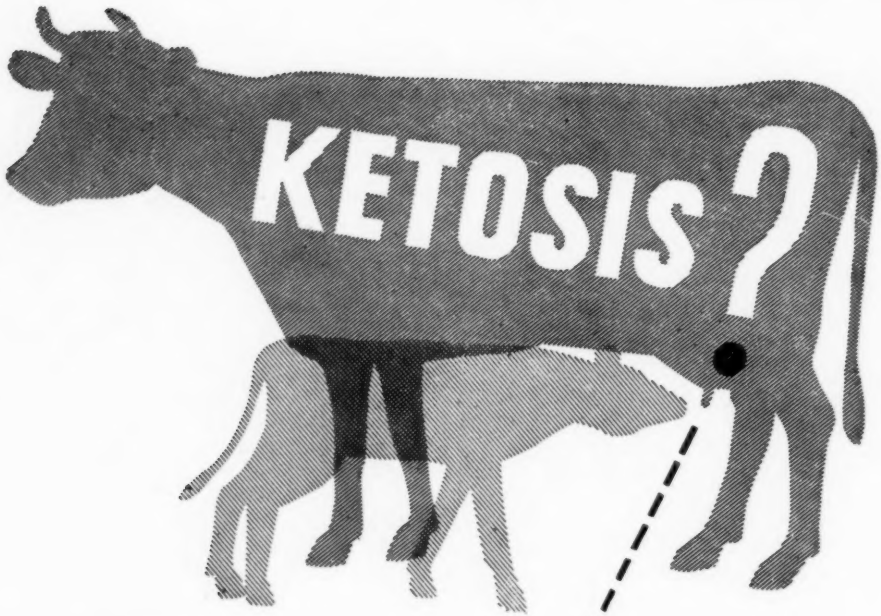
President:

E. R. Callender, Esq., O.B.E., M.R.C.V.S.

VOL. 69 NO. 49 PART TWO ISSUE NO. 4157 1129-1408 DECEMBER 7th 1957



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Some Immunological Phenomena in Parasitic Infections

BY

E. J. L. SOULSBY

Department of Animal Pathology, University of Cambridge

Introduction

IN order to live more or less permanently within a host a parasite must be able to contend with a variety of mechanisms which the host may bring to bear against it. Some of these may be factors with which the host is naturally endowed, whilst others may be acquired as the result of the parasitic infection. The former may be referred to as factors in natural immunity and the latter as those in acquired immunity. It is with the latter that this discussion will principally deal, but a brief indication of some of the mechanisms which may explain natural immunity or resistance may adumbrate future explanations of immune mechanisms.

Normal Mechanisms

There are examples in hosts other than mammals and birds where resistance to parasites can be ascribed to specific morphological and physiological features, but in mammals natural immune mechanisms can at times be referrable to specific factors in body fluids. This is instanced in the case of trypanosomes where it has been found that the normal serum of several animals has an antagonistic action on certain species of this organism (Laveran, 1902; Culbertson, 1935). Thus normal human serum destroys almost all pathogenic trypanosomes with the exception of those infecting man, namely *T. gambiense* and *T. rhodesiense*, the causal agents of sleeping sickness. This action may explain why man is not infected by the pathogenic animal trypanosomes. A similar reaction occurs when the cercariae of many species of flukes are exposed to the normal serum of a wide range of animals (Standen, 1952). In many cases animals possessing such a normal serum action against a particular trematode cercaria fail to become infected by the cercariae (Culbertson, 1936). This property is not restricted to mammals since mucus of certain fish exerts a lethal action on trematodes, the activity being directly proportional to the resistance of the fish to infection by the trematode.

It is probable that these reactions of normal sera on a wide variety of parasites are similar in nature to those investigated by Mackie and Finkelstein (1931) with reference to bacteria and may well represent the manifestation of the activity of a limited group of substances. Nevertheless, investigations in this direction and also along the lines of the work carried out by Robertson (1934 and 1939) on the action of immune serum on free-living ciliates may give some hint as to the mechanisms which render organisms susceptible to immune mechanisms.

Immune Mechanisms

It is, however, the mechanisms of acquired immunity which are of greatest interest both from the practical and theoretical standpoints. It was the early work concerned with the serological response to bacteria which stimulated research into such phenomena in parasitic infections and pioneer work by Ghedini (1906) and Casoni (1911) and others introduced tests for the diagnosis of parasitic infections, which are still used as aids in human medicine.

Some time elapsed, however, before marked interest was taken in the effects of immunity on parasites and despite the early recognition by Smith and Kilbourne (1893) that cattle recovered from Texas Fever (*Babesia bigemina*) were immune to subsequent attacks only occasional reports were made indicating that man and animals became immune following infection by parasites. Parenthetically it is interesting to note that Smith and Kilbourne were the first to show that immunity depended on the persistence of the parasite in a latent form within the host, a condition which has been designated "premunition." Notwithstanding the slow advance by contemporary standards, by the end of the second decade of this century it was demonstrated unequivocally for example that the immunity was acquired to pathogenic trypanosomes (Laveran, 1911), avian malaria (Moldovan, 1912), poultry coccidiosis (Beach & Corl, 1925) and *Haemonchus contortus* infections in sheep (Stoll, 1928). Some subsequent demonstrations of acquired immunity have occurred in trichostrongylosis of sheep (Taylor, 1934, and Gibson, 1952), trichostrongylosis of rabbits (Sarles, 1932, and Michel, 1953), *Dictyocaulus filaria* infection in sheep (Kauzal, 1934), *D. viviparus* infection in cattle (Rubin & Lucker, 1956) and *Strongyloides papillosus* infection in sheep (Turner, 1956). For extensive accounts of parasitic infections in which immunological phenomena have been recorded the reader is referred to Taliaferro (1929) and Culbertson (1941).

Self Cure and Protection

In general the effects of immunity on parasites, which is a main thesis at present, is to result in one or more of the following manifestations, namely complete refractoriness to reinfection, the elimination of existing infection, complete or partial inhibition of development and inhibition of reproduction. An appropriate point of departure for the purposes of this discussion is the work of Stoll (1928 and 1929) who recorded the phenomenon of "self cure and protection" in sheep exposed to stomach parasites. Stoll infected one of two lambs with *Haemonchus contor-*

tus and placed them both on pasture. Within 10 weeks faecal egg counts rose to high levels and then there was a dramatic fall in egg counts to negative levels within two or three weeks; this was associated with loss of worms ("self cure"). Subsequently, despite frequent reinfection with large numbers of infective larvae, the lambs remained refractory ("protection"). It should be stated that the term "self cure" is perhaps a misnomer since Stewart (1950) has shown experimentally that a dose of larval stimulating the "self cure" mechanism may ultimately progress in development and kill the animal. Nevertheless, under natural conditions this eventuality may be of less importance.

Stoll's results are essentially applicable on a flock basis and particularly so in a flock of sheep undergoing the "spring rise" phenomenon. This "spring rise" was extensively investigated by Morgan and his co-workers (1947, 1950, 1951, 1952) in Scottish hill sheep and has since been noted in lowland sheep by Crofton (1954). The essential facts concerning this are that during spring a marked increase in egg output occurs in sheep and Morgan *et al.* (1951) found this to be associated with an increased burden of worms. Parallel studies, on a flock basis, with serological tests indicates that the termination of the

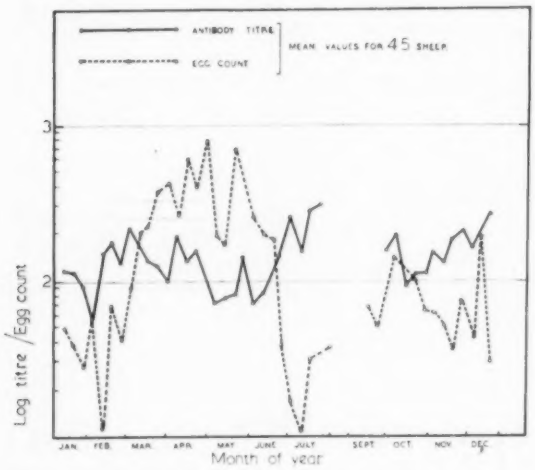

FIG. 1.—Mean antibody titre and mean number of eggs per gramme of faeces of 45 sheep throughout the year.

"spring rise" is associated with a marked elevation of antibody titre (Soulsby, 1957c) (see Fig. 1). Subsequent to this termination, which has all the characteristics of a group "self cure" mechanism, the level of egg output during late summer and autumn is low despite the fact that during this period the pasture populations of infective larval stages are high (Crofton, 1949). The flock has thus developed a measure of "protection." Ross (1932) has stressed that the immunity elicited by a previous infection is of a transient nature and in the absence of reinfection any substantial degree of protection will quickly wane. It is to be stressed that the results presented above are applicable to the adult members of the flock. The introduction of susceptible animals into the flock during the period of protection may result in clinical disease. In fact lambs of the flock, not having undergone the "spring rise" and the "self cure" mechanism, reflect the high pasture burdens of larvae (Crofton, 1955). It is well known that it is usually the juveniles of the flock which suffer clinical helminthiasis during this period.

Mechanism of Self Cure

For further analysis it is convenient to separate the phrase "self cure and protection" and to consider each entity individually. This is an arrangement of convenience. The bases of the two entities are probably identical and it is obvious that the host is the architect for both mechanisms, but the manifestations differ in that one is principally an acute reaction affecting the host whereas the other, "protection," is a reaction mainly affecting the parasite.

"Self cure" in sheep nematodes, as investigated by Stewart (1953), consisted of a marked hypersensitive response in the abomasal or intestinal mucosa following the ingestion of infective larvae. Associated with the reaction there is a significant rise in blood histamine and the "self cure" reaction can be suppressed if antihistamine drugs are given at the anticipated time of the reaction. Injection of infective larvae in the abomasum of sensitised sheep produced typical "self cure" (Stewart, 1955). Following the phenomenon antibody levels rise markedly. This point is important since it indicates that the presence of high levels of *circulating* antibody are not responsible for the mechanism. A similar situation exists in the adult phase of *Trichinella spiralis* infection in rats, where the majority of adult worms are generally eliminated 11 to 14 days after infection (Larsh, Gilchrist & Greenberg, 1952), the elimination being associated with marked inflammation and cellular invasion of the bowel mucosa (Larsh & Race, 1954). In animals immunised by a previous infection the cellular reaction develops more rapidly and there is a greater loss of worms at an earlier period (Larsh & Race, 1954). If such rats are treated with cortisone, which has a mitigating effect on hypersensitive states, then the adult *T. spiralis* infection can exist for much longer periods (Coker, 1955).

The onset of the "self cure" mechanism in *Trichostrongylus retortaeformis* in rabbits has been shown by Michel (1952) to be related to the severity of the infection created and may be construed as the amount of antigen made available for the initiation of the process. The antiparasitic nature of the "self cure" reaction has not yet been determined but Schmidt (1952) has suggested a mechanical basis, in that the allergic reaction in the mucosa of the bowel results in exudation, leucocytosis and spasm of the smooth muscles of the bowel wall resulting in ejection of the parasite burden. Indeed, Stewart (1955) has reported marked contractions of the sensitised abomasum when it is injected with larvae. Though this is an attractive explanation it is possible that other non-specific mechanisms play an important part, in particular factors which alter the micro environment of the parasite. It is known, for instance, that inflammatory processes have a tendency to decrease

the local oxygen tension (Campbell, 1931) and it is conceivable that the local inflammatory response in the bowel of sheep undergoing "self cure" may so interfere with the normal physiological requirements, and consequently the metabolism of the helminths, that initially egg production is inhibited and subsequently the worms are unable to maintain themselves in such an environment.

The "self cure" reaction has been noted in other helminth infections. Of particular interest is the phenomenon in parasitic bronchitis (Wetzel, 1948) and which, according to Michel (1954), may be much of a Pyrrhic victory for the host since the clinical entity of "fog fever" may supervene. A condition analagous to "self cure" has been noted in pigs infected with *A. lumbricoides* when reinfection occurs (Taffs, 1957). In addition to a drop in egg output and rise in antibody titre Taffs has also noted that a marked increase in infertile eggs occurs.

The hypersensitive basis of the "self cure" mechanism is not unexpected since helminths appear particularly adept in producing such states. This sensitivity is utilised in the human field for valuable diagnostic tests and in parasitic infections of veterinary importance skin tests can be used to detect sensitisation by parasites. Thus sensitisation caused by liver fluke (Sievers & Oyarzun, 1932, and Soulsby, 1954), ascarids (Ransom *et al.*, 1924; Wilkening, 1937; Soulsby, 1952, 1957b) and lungworms (Hudson, 1951 and Soulsby, 1952) can be detected by skin tests but these are not generally applicable as diagnostic aids in this country. Indeed in the case of *A. lumbricoides* infection in pigs positive skin and other serological tests cannot be correlated with the presence of adult worms (Soulsby, 1952), a similar situation being applicable in humans (Coventry & Taliaferro, 1928).

Retardation of Development

This increased reactivity of the body to helminth infections is seen in local lesions where a rapid mobilisation of cells occurs, the eosinophilic leucocyte being particularly in evidence. Such local lesions were at times so impressive that it has been postulated that a purely local immunity existed in certain helminth infections but this has not been justified in the light of further investigations. Within the local lesion, at the site of penetration or elsewhere, the parasite or its larval stages suffer death and disintegration: which one would consider as the natural consequence of a foreign organism in a host. Nevertheless there are many instances where the larval stages of nematodes may remain dormant in the tissues and subsequently awake and become mature. This is well illustrated by the findings of Gibson (1953) who observed that the removal of mature worms from the large intestine of horses allowed a new population of worms to develop from larvae which had been dormant in the mucosa. The dormancy of helminth larvae in the mucosa of the intestinal tract has been dealt with by Sommerville (1954) with respect to *Ostertagia* sp. and his findings may partly explain the initiation of the "spring rise" phenomenon in sheep. Kotlan (1949) has designated this phase the "histotropic phase" of a parasite's life cycle and Taylor and Michel (1953) have discussed it in relation to retarded development of *D. viviparus* and other worms.

The retardation of development is one of the essential processes in immunity directed against parasites and is one of the aspects of protection in the context "self cure and protection." It is not unreasonable to assume that almost all effects detrimental to the parasite are essentially an interference with its metabolism. At present our knowledge is based on the manifestation of such interferences and we still have to inquire into the essential processes which are being interfered with.

One of the most interesting observations as regards the effect of immunity on parasites was the observation by Sarles (1937) that when larvae of *Nippostrongylus muris*, a parasite of rats, were placed in homologous immune serum precipitates appeared around the natural orifices of the larvae, namely the mouth, excretory pore and anus. This reaction has since been observed in a number of nematode infections including hookworms (Otto, 1939), *T. spiralis* (Mauss, 1940) and *A. lumbricoides* (Oliver-Gonzalez, 1946). Fig. 2 illustrates such a reaction occurring at the excretory pores and the mouths of *Ascaris* larvae placed in immune serum. The author has observed that the reaction is most evident at the excretory pore which may indicate that the materials emanating from this opening represent the major part of the antigenic material available. These "circumlarval" precipitates may also be seen *in vivo* in sections in the case of *N. muris* (Taliaferro & Sarles, 1939) and also in *Ascaris* larvae attempting to migrate in an immune host (see Figs. 3 and 4).

Though it is likely that these precipitates function in some way as mechanisms reducing the vitality of the parasite their role is not yet clear. Mauss (1940) showed that when *T. spiralis* larvae were exposed for one hour to immune serum they lost 60 per cent. of their infectivity. Extensive work with *T. spiralis* by Oliver-Gonzalez (1941) has shown that antiserum, which when given passively will protect animals against both the adult and larval stages of this infection, can be produced by the infection of animals with the parasite. The protective property of the serum cannot, however, be removed by absorption with dried and pulverised adult or larval materials despite the fact that conventional serological tests are rendered negative by this procedure. Furthermore, vaccination of animals with dried parasite materials does not induce "protective" antibodies though antibodies detectable by the conventional serological tests are raised. Thus antibodies exist which are protective in character but are not absorbable by conventional methods. Reports of other "non absorbable" antibodies have been made with respect to *Cysticercus fasciolaris* and *Trypanosoma lewisi*. In the case of *C. fasciolaris*, which is the intermediate stage of the cat tapeworm *Taenia taeniaeformis*, Campbell (1938) has stated that there exists an antibody, occurring early in infection ("early" antibody) which can be absorbed by dried worm material and can be induced by vaccination with such material.

The function of this antibody is to protect the animal against the invading hexacanth embryo of the tapeworm egg. Later in infection, however, a second antibody ("late" antibody) appears which results in the death of the established, and frequently quite large, parasite cyst. This "late" antibody cannot be absorbed by worm material and cannot be induced by vaccination. Campbell suggests that the second antibody is stimulated by the metabolic excretions and secretions of the parasite.

Inhibition of Reproduction

Probably the best example of non-absorbable antibodies in parasitic infections is with the ablastin antibody of *T. lewisi* discovered by Taliaferro (1924) and extensively investigated by W. H. and L. G. Taliaferro (see Taliaferro, 1948). This antibody is exquisitively specific in its action which has as its sole function the inhibition of reproduction of the trypanosome. The ablastin cannot be absorbed by reproducing trypanosomes and such forms exposed to it continue division quite readily when placed in a new host. In other words the *continued* presence of the antibody is essential if all mitotic division and growth are to be inhibited. It is to be noted that the destruction of the trypanosomes is brought about by a separate and distinct lytic antibody which can be absorbed and when trypanosomes sensitised to this lytic antibody are placed in a normal host the organisms are destroyed. Biochemical studies on *T. lewisi* populations by Moulder (1948) have shown that the presence of ablastin antibody in a population of trypanosomes changes the metabolism of glucose from that characteristic of reproducing trypanosomes to that characteristic of an adult population. The ablastin of *T. lewisi* has features in common with the ablastin seen in *T. duttoni* infection (Taliaferro, 1938), each antibody inhibiting reproduction of the heterologous trypanosome to some extent. Chandler (1953) has suggested that these two ablastins are a response to a common metabolic system responsible for nuclear and cytoplasmic division. Very recently Thillet and Chandler (1957) have been able to collect the "metabolic products" of a population of dividing *lewisi* trypanosomes and to produce a marked immunity by vaccinating animals with these; proof that the body of the parasite is not necessary for the production of ablastin antibody at least. The net effect of the studies of non-absorbable antibodies is to suggest that the specific antigen is not in the absorbing material since this usually consists of dead and denatured parasite tissues. It rather suggests that living organisms are necessary for neutralisation and that to produce antagonistic effects on the parasite the antibody would need to be there continuously as if it were interrupting a kinetic system rather than merely sensitising a static entity.

Anti-enzyme basis of immunity

Great stress has been laid on the importance of these so-called "metabolic products" produced by helminths and it is generally accepted that they play an important part in immunity and Chandler (1953) is particularly in favour of an anti-enzyme basis for explaining immunity to parasites. This theory is very attractive and would explain why immunity induced by methods using dead and disintegrated parasites is vastly inferior to that occasioned by active infections with living forms. It is obvious that the residue of enzymatic protein must be small in dead material and though a marked antibody response to the body proteins of the parasite occurs only a low degree of protection is afforded against subsequent infection.

It is fairly certain that a vast complex of enzymes must exist in living organisms and for the purpose of this discussion two main types can be considered, namely, the "internal" and the "external" enzymes. The internal are those which are responsible for the metabolism of the parasite such as those responsible for carbohydrate metabolism in which the Embden-Meyerhof sequence has been shown to exist (von Brand, 1952). Some of the external enzymes may be concerned in the preparation of food for ultimate utilisation by the parasite; others for the invasion and migration through the tissues. The latter type have been demonstrated in the invading cercariae of *Schistosoma mansoni* and the larvae of *Strongyloides ratti* (Lewert & Lee, 1956) where a collagenase-like enzyme assists in the penetration of the skin. Hyalurodinase has been demonstrated in *Entamoeba histolytica* (Bradin, 1953) and a hyaluronidase-like enzyme has been demonstrated in *S. mansoni* cercariae (Stirewalt & Evans, 1952). These types of enzymes may possibly be likened to the aggressins of bacteria and it is most likely that they will be expelled from the oesophageal glands of helminths. Thorson (1956) has shown that the secretions from the oesophageal glands of dog hookworms contain proteolytic enzymes the activity of which can be inhibited by serum from dogs immune to hookworms. Oliver-Gonzalez (1941) has demonstrated that two different antibodies are present in *T. spiralis* infection being initiated by the two phases of the parasite (in the adult, bowel phase, and the larval, muscle phase). Each antibody possesses a definite protective effect on the stage which produced it and little protective action on the other phase. He suggests that these infections may be due to a variation in enzyme requirements of the various stages, the enzyme system being changed for each new substrate met with (*e.g.*, from the bowel wall to the muscle fibres). The phenomenon of adaptive enzymes in bacteria is well known but it has not been observed in parasitic nematodes.

Whether the materials which flow from the excretory pores of helminths are "external" enzymes is not known. It is conceivable that they are in fact waste end products from the "internal" enzyme moderated metabolic systems and whether an antibody against such products will inhibit the precursors is a matter of conjecture. The mere presence of a cap of precipitate (as shown in Fig. 2) at an orifice from which metabolic products flow forth may not be of immediate importance to the parasites since these can be relatively easily dislodged by the parasite. It has been suggested, for example, that precipitates occurring on the vulva of worms mechanically obstruct the passage of eggs, and similarly precipitates on the

excretory pore block the excretory system (Culbertson, 1941). It is more likely, however, that the essential antagonistic mechanism consists of a penetration of the antibody to within the parasite body to produce an interference with inner mechanisms.

Since these so-called "metabolic products" are given off by parasites they resemble, in some respects, the exotoxins of bacteria and it is well known that such toxins are agents which stimulate a high degree of immunity. If the metabolic products are of importance in "protective" immunity then it should be possible to induce immunity by vaccination with such products. Some degree of success has been obtained by Thorson (1951) with *N. muris* infection in rats and with *T. spiralis* in mice (Campbell, 1955). Fig. 5 shows the growth of *Ascaris* larvae in guinea-pigs immunised with larval metabolic products compared with the growth in non-immunised animals.

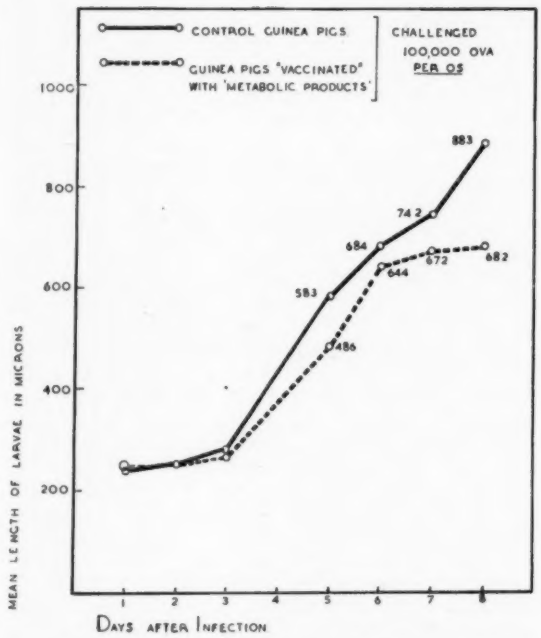

FIG. 5.—Mean lengths of larvae derived from a challenge infection of 100,000 *A. lumbricoides* ova *per os* in a control group of guinea-pigs and a group immunised by subcutaneous injection of the "metabolic products" of *A. lumbricoides* larvae.

The collection of metabolic products from larvae presents many technical difficulties and the results obtained by such methods may be quantitatively limited by the amount of material which can be made available. This early evidence that metabolic products can act as immunising agents indicates that living worms must be present before substantial immunity can be produced. This is not applicable in the case of the intermediate stages of cestodes where immunity can be produced by vaccination with dried and pulverised worm antigens.

Immunisation Procedures

It is possible with *A. lumbricoides* infection in guinea-pigs to alter the normal migration route by injecting infective eggs subcutaneously. Here a minority hatch and the larvae wander locally in the tissues and a few reach the lungs. Doses of eggs substantially in excess of those which would be lethal by the oral route can be administered in this way. With such a procedure the animal has made available to it the products associated with actively living, growing and migrating larvae (Soulsby, 1957a). Fig. 6 shows the growth of larvae in a group of guinea-pigs vaccinated by this method compared with another group vaccinated with ground-up fresh adult worm material and a control group of guinea-pigs. It is obvious that this vaccination procedure is efficient. This method may well be of use in other helminth infections where the larval stages undergo a marked migration in the body.

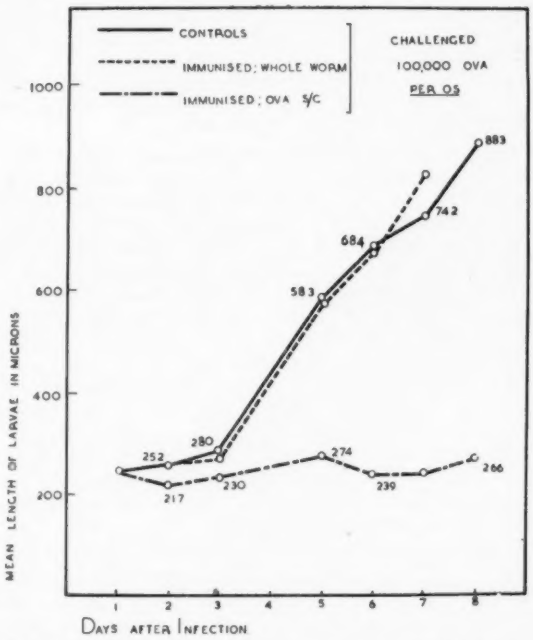

FIG. 6.—Mean lengths of larvae derived from a challenge infection of 100,000 *A. lumbricoides* ova *per os* in a control group of guinea-pigs, a group of guinea-pigs immunised with an extract of fresh adult whole worm and a group immunised by subcutaneous injection of embryonated *A. lumbricoides* ova.

The above is an example of allowing an infection, but under control, to immunise an animal. Another well-known example, with practical application, is that in coccidial infection, particularly *Eimeria tenella* infection. In this case the various stages, particularly the pathogenic second generation schizont, are allowed to develop in a controlled manner (*i.e.*, under the influence of coccidiostatic drugs). Such a method will allow the establishment of a high degree of resistance which cannot be paralleled by methods using attenuated or killed material.

A further method of interest and which may have practical applications, is that of attenuating the infective larvae of nematodes so that they are unable to develop to the mature state. This method, if applicable to parasites other than those mentioned below, may have wide implications both from the tactical and strategic point of view. Attenuation can be created in *T. spiralis* by treating infective larvae with X-rays thus rendering the adult worms sterile. An infection created by such treated larvae will produce a definite degree of immunity to reinfection with non-irradiated larvae (Gould, Gomberg, Bethell, Villell, & Hertz, 1955). An excessive dose of X-rays is to be avoided since the maturation process is interfered with and little or no immunity results.

It is obvious that many of the studies of parasites have of necessity been carried out in the small experimental animals and it is necessary for some of these studies to be transferred to the larger domestic animals especially in the case of the intestinal parasites and the lungworms. The findings in laboratory animals are probably applicable, with reservations, to the larger animals.

Adaptation of parasites to the host

It is to be emphasised that parasites, and in particular the helminths with which this discussion is primarily concerned, are complex metazoan organisms, animals, in fact, possessing systems of metabolism not unlike those of the body of the host which they parasitise. The parasite in the tissues or in the bowel is not an inert mass of protoplasm. Beneath the cuticle of the parasite complex mechanisms are constantly at play, some of which are only indistinctly known whilst many are still only guessed at. To give illustrations, one must attempt to conjecture the protein synthesis which will allow a single *Haemonchus contortus* female to lay 5,000 eggs daily (Martin & Ross, 1934) or for the population of *T. equiperdum* to increase from 20 million organisms per 1 ml. of blood to 4 billion per 1 ml. in 100 hours in a rat (Hoppe & Chapman, 1947).

Such complex mechanisms, and it is not suggested that other infectious agents are less complex, may easily fall prey to antagonistic substances directed against them, unless the parasites are endowed with a special mechanism for protecting themselves or more especially the population. A valuable field of study, therefore, is the mechanisms by which parasites tolerate their hosts.

Perhaps the protozoa give the best examples of parasite populations adapting themselves to their hosts. This is particularly evident in the pathogenic trypanosomes where relapse strains can repopulate an animal following almost total decimation of a previous population: the new population being unaffected by the antibody produced against their forebears. Cantrell & Betts (1956) in their studies on *T. equiperdum* have estimated that as few as one trypanosome with a different antigenic structure in a population of up to 20 million antibody-susceptible trypanosomes is sufficient to allow for a relapse strain to occur by the method of selection. Whether this is the only method which can occur from the immunological point of view is not known. In drug resistance studies, which in some respects show common characteristics with immunological phenomena, selection is considered a possibility but it is now generally conceded (von Brand, 1952) that where resistance to drugs in concentrations many times that necessary to kill the individuals of a susceptible population occurs, then a fundamental change is necessary which Eagle and Magnuson (1944) have suggested is a genetic mutation. The studies being carried out on drug therapy and particularly in the sulpha drugs and antibiotics, where the therapeutic effects are those of an interference with the metabolism of organisms may at some time assist greatly in the understanding of immune mechanisms.

Becker (1953) has discussed the means by which parasites protect themselves from their hosts and suggests that the polysaccharide components of organisms may play an important part. He points to the examples of the capsules of bacteria such as *pneumococcus* type III and suggests that analogous mechanisms may occur in metazoan parasites. The cuticle of a helminth parasite deserves special mention since it is this presumably which protects it from being digested. The cuticle may also be a defence mechanism against immunological mechanisms since Taliaferro (1940) has expressed the opinion that the cuticle of the living worm is impervious to antigenic materials. This view was modified by Oliver-Gonzalez (1943) who suggested that although the cuticle was non-reactive in immune animals, antigenic materials may diffuse through it, particularly where the parasite had been previously damaged by immune action. It is thought that the cuticle is so insoluble in the living worm that little or no reaction occurs with it even in a high titred, artificially produced anti-cuticle serum. The origin of anti-cuticle antibodies during infection is explained as being due to death and disintegration of the worms. If this is so then a migrating larva or an egg-laying female would be unable to stimulate the host to produce immunity except by the material extruded from the parasite in the form of "metabolic products." This could be extended to apply also to certain blood protozoa. It could be envisaged that the surface layers of the protoplasm are non-antigenic in the living forms and only on the death of the parasite does the host become immunised against the protoplasm of the parasites. It is interesting in this connexion to refer to the work of Desowitz and Watson (1953) who have postulated that *T. vivax* in sheep is able to draw some specific protective substances from the host's blood in order to escape the action of antibodies which are present along with the infection and which will agglutinate and kill the trypanosome if washed free of sheep serum. This blood factor is probably identical with a substance in sheep serum which, when injected along with *T. vivax* into rats, will cause an infection in this otherwise refractory host. The phenomenon is akin to the "sparing action" of duck serum on *Plasmodium lophurae* infected duck erythrocytes injected into chickens (Becker & Schwink, 1953).

Unusual Reactions

It is unavoidable that in studies on immunological phenomena to parasites many reactions have been found for which no adequate explanation at present exists. There is, for example, the observation of Oliver-Gonzalez (1954) that many parasites possess a substance which is closely related to the blood group substances of man and animals. The infection of rabbits with parasites such as *A. lumbricoides, F. hepatica* and *T. spiralis* results in a marked elevation of anti-blood group A antibodies. An antigen similar to the human A substance has been suspected in the malarial parasite of man, *Plasmodium falciparum* (Oliver-Gonzalez & Torregrosa, 1944), and this antigen has been regarded as the basic cause of the haemolytic manifestations characteristic of malignant tertian malaria. The mechanism suggested is that of the stimulation of antibodies against the parasite A-like substance which then (cross) react with the patient's own A red blood cells (Gear, 1946). Foy (1948), however, has cast doubts on this mechanism. An even more interesting observation made by Oliver-Gonzalez (1953) is that substances from parasites, particularly blood group substances, may become fixed to red cells and so alter the specificity of the red cell.

Since these blood group-like substances occur in parasites which are of some importance to veterinarians it would be of interest to know whether the possession of certain blood groups by animals conferred any benefit or any susceptibility on the animal as far as parasitic diseases are concerned. Perhaps further studies with the gastro-intestinal nematodes of cattle and sheep would reveal the existence of blood group substances thus explaining to some extent why iso-antibody titres in grazing cattle fluctuate markedly during the seasons of the year (Stone, 1956).

In conclusion it can be said that immune mechanisms play a substantial part in limiting parasitic disease and ideally the ultimate goal is to utilise these for control. Immunisation by vaccination or by carefully controlling infection is the clinical approach to such control measures. This approach has been successful in coccidiosis of poultry and in experimental animals. With respect to the latter point the warning of Theobald Smith (1934) may be applicable here in that "the experimental method must not let too many machines get between it and the whole and must find some way of putting the fragments surgically removed for experimental purposes back into the whole."

With the increased interest now being taken in immunological phenomena in parasitic infections it is to be hoped that the fragments so removed for experimental study will be assembled into the whole more rapidly and efficiently to produce satisfactory immunisation procedures for the control of the more important parasitic diseases in this and other countries.

Summary

Immunity to parasites may be manifested by complete refractoriness to infection, the elimination of an existing infection, depression of growth and development, or, in the case of helminths, the inhibition of egg production.

The elimination of a parasite population is exemplified by the "self cure" phenomenon in the case of nematodes, whereas with protozoan parasites, for example, trypanosomes, an antibody with lytic properties is concerned.

During an infection, antibodies are demonstrable against the body tissues of the parasite and in certain instances these antibodies play a part in the destruction of the organism. However, in nematode infections such antibodies in many cases possess no protective properties. The mechanisms of an antagonistic action appear to be directed against substances associated with living parasites and some success has attended the artificial immunisation of animals with "metabolic products" of living parasites. Where a parasite infection can be adequately controlled it is possible to induce a marked degree of protective immunity to the parasite.

In addition to mechanisms resulting in protection of the host other phenomena occur, some of which may explain the natural resistance of various animals to specific parasites. Other of the phenomena may benefit the parasite or may be detrimental to the host.

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THE SPEAKER'S INTRODUCTION

Dr. Soulsby, in presenting the paper, said that an attempt had been made to indicate how an animal dealt with a pathogenic parasite and particular emphasis had been laid on the effects on the parasite. In studying the effects it was hoped to elucidate the mechanisms of protection, since it was necessary to know where the main site of action on the parasite occurred. From that information it might then be possible to devise artificial means of immunisation which would be concentrated specifically at the right stage at the right time.

The subject of immunity to parasites was relatively new, and there were still only a handful of people in this country carrying out work on it. The work was hampered to a great extent by the difficulty of handling such parasites, and also by the lack of knowledge regarding their physiology. It was not possible, for example, to culture nematodes of animals successfully and, furthermore, their multiplication was a process which depended on their reaching adult life. Obtaining materials for work was not as easy as culturing bacteria in test tubes.

It was well known that in the majority of cases once an animal had suffered parasitism it was partially or completely refractory to reinfection—a phenomenon easily observable in domestic animals in the field. The question arose as to how such immunity worked. It was relatively easy to demonstrate that antibodies were concerned, probably to a very great extent, but it was less easy to determine their action on the parasite. As mentioned in the paper, retardation of development was an essential process in immunity and one aspect of that the " histotrophic phase " in nematode infections had now rather complicated the outlook both from treatment and control. To give an example of that, Dr. Roberts, of Queensland, had shown that with *Haemonchus placei,* a parasite of cattle, repeated reinfection might build up a large population of dormant larvae in the mucosa, those being somehow depressed by the presence of adult worms. If those adult worms were removed by treatment with phenothiazine, the larvae then developed to give rise to severe infection. In fact, phenothiazine might be used to create a good infection. How was it possible to reorientate one's ideas when one of the well-known and tried drugs had the opposite effect to that expected?

During the course of development within the host a nematode generally underwent certain changes of life which were referred to as "moults," that is, the change from one parasitis stage to another. Those moults must involve some not uncomplicated reorientation of metabolism, and also involved the development of digestive and reproductive systems. Frequently also those moults coincided with a change of habitat. It would be permissible to speculate that those periods might well be critical to the parasite and that they might well be the most susceptible periods of the life cycle at which immune mechanisms might act.

Evidence was being accumulated that the period of the moult in nematodes was in fact an important period at which immunity was stimulated, and also when immune mechanisms had their most advantageous effect. In *Ascaris,* for example, it had been found that although a certain amount of growth of larvae could occur prior to the moult, in the vast majority of larvae moulting could not be accomplished. In addition it had been found that the moulting period was the time at which to expect large amounts of antigen to be released. Professor Rogers, of Adelaide, had been able to isolate " exsheathing fluid " from nematode larvae, and experiments were in progress to ascertain if that fluid had any immunising properties. If such work were successful, it might well be possible to immunise against a particular moult disregarding all other stages.

What were the practical implications of such work as that? The author suggested that many applications were but a short while ahead. Mention would be made during the week of a procedure which at last might well give the answer to husk. Experiments here with *Ascaris* had shown that it was possible to immunise against that worm. One could point to the advantageous use of immunisation to avoid the "spring rise" in sheep and mitigate subsequent parasitism in flocks. The use of controlled grazing with a view to producing immunity to intestinal nematodes of sheep had many practical applications, and Dr. Taylor had admirably explained, in a previous address at the Second British Caribbean Veterinary Congress, how immune animals might be used very much as scavengers to mop up infective stages of parasites.

Probably the greatest scope for immunological methods for the control of parasitic disease lay not in this country, but abroad in the tropical and sub-tropical areas. One had but to bring to mind the appalling disfigurement of filariasis and the blindness of *Onchocerca* to realise that any immunisation procedure which would eliminate those would be of direct benefit to mankind. From the veterinary stand-

point, protozoal diseases in the tropics were particularly important, and it was perhaps noticeable that the paper was weighted very much on the helminth side. It was hoped that those at the meeting with experience of immunity in protozoal disease would contribute to the discussion.

The Openers

Dr. A. M. Dunn, in opening the discussion, said that it might be worth while considering some of the points which the author had raised in direct relation to the grazing animal.

When a series of worm egg counts on an animal at pasture was examined, it was observed that there occurred a series of fluctuations, and those fluctuations were not random but could be interpreted in terms of immunological reaction on the part of the animal. As a rule there were a number of lesser fluctuations, and one major fluctuation. This was, of course, the spring rise, which was still one of our most persistently puzzling immunological phenomena. As was known, it was an annual occurrence, lasting for 6 or 8 weeks, and the increased egg count was due to a positive increase in worm burden. The causes of that increase had occupied those concerned for a number of years, and new explanations were constantly coming forth.

It might be recalled that the original contention was that it was simply an exhibition of debilitation on the part of the animal so reducing its resistance at the end of winter, that it was unable to cope even with the small number of larvae which it picked up. Since then the original theory had been under more or less steady fire and, lately, as the author had pointed out, the principle of larval retardation was being applied to it. It certainly seemed much more feasible. Larval retardation or inhibition was an old phenomenon which was being found to have increasingly wide applications in present-day helminthological research.

It implied, of course, a state of equilibrium between host and parasite—that the host could prevent larval development in a certain state of resistance and, conversely, that the larva could suspend its own development until there was an alteration in the state of the host's resistance. It was, therefore, a very unstable equilibrium, and it could easily be upset by stress of some sort. It was found that the theory fitted very well, assuming the presence of the inhibited larvae, because it was at the beginning of spring that the animal was subject to the greatest number of debilitating influences. For example, so far as parturition was concerned, it had been shown that early lambing ewes tended to have an earlier spring rise than late lambers. Then with regard to climate, the spring rise in two groups of sheep was followed over a period of 8 years, and it tended to be much exaggerated following a severe winter, being almost twice as high in the springs following the winters of 1947 and 1951, which were particularly severe, than in other years. Nutrition was, in his view, the most important contributory factor. If the bodyweight curve of an average young hill sheep were examined over the winter, it was found that it emerged from the winter, at one year old, actually lighter in weight than it was at 6 months. It seemed highly likely that most of the reduction in resistance could be attributed to nutritional effects, and that the others were simply superimposed upon it. Therefore, in general terms, the spring rise appeared to be a stress phenomenon, and the necessary conditions to precipitate it were most likely to be found in late winter.

The other fluctuations in egg counts could be attributed to repeated self-cure and reinfestation, and indicated therefore a repeated turnover in worm population.

Slide 1. Showed a graph illustrating the sequence of events in a single animal at pasture, with antibody fluctuations superimposed upon egg count. It was clear that most of the increases in egg count could be referred to prior increases in antibody level, at intervals approximating the prepatent period of the gastro-intestinal worms, and indication of repeated larval intake.

One interesting feature was that the spring rise did not differ from the others in that respect, and this suggested a rather more complicated process than was supposed, arising both from larval intake and from the emergence of inhibited larvae.

If the animal were considered in relation to its pasture environment, one could perhaps attempt to fill in some more of the details.

Slide 2 showed mean egg counts of a group of sheep on pasture with the pasture larval population, and it helped to show what he meant when he said that the spring rise picture was not simple. It showed that the phenomenon really occurred in two phases—that the first phase of increased egg output probably arose from the emergence of retarded larvae, but that, resulting from that, there was a heavy pasture contamination, and the intake of larvae from that provoked a partial self-cure—the "trough" or "notch" effect and those larvae then developed to produce the second phase of the spring rise. A "notch" on the ascending side of the spring rise was in fact a very common feature in most of the serial sampling which had been done over the past years.

If the egg count and pasture larval burden were broken down in terms of the commonest species present, a suggestion of a prolonged series of events was found. First there was the first part of the spring rise produced, one supposed, by the emergence of inhibited larvae and consisting of Trichostrongylus and Ostertagia with a few Haemonchus. That was followed by a pasture contamination, and followed in turn by the second part of the rise, resulting from the contamination. The interesting feature of a breakdown of that sort was that it showed that Haemonchus predominated in the second part. At one time it was assumed that, since Haemonchus required a much higher temperature for complete development in its free-living stages—Dinaburg had placed it as high as 65° F. although that was now being questioned—it would therefore not reach infective stage until much later in the spring than the others, and hence later in the spring rise.

It appeared from that evidence, however, that the very large numbers of Haemonchus eggs could be explained in terms of biotic potential, remembering that a female Haemonchus laid about a hundred times as many eggs as a Trichostrongylus and in the end completely overshadowed it.

That description was, of course, very much over-simplified, but even from a small survey of that sort a variety of points was bound to arise, and in the interests of the general discussion he would confine himself to two which he gladly passed on to the author for his consideration.

To think again for a moment of the significance of larval retardation in the field, for a long time attempts were made to eliminate or to reduce the spring rise by prophylactic dosing with anthelmintics, as close as possible to the origin of the rise, just before lambing, with very doubtful success. If the theory of larval inhibition were true, then it was necessary to look a long way further back for the point of control than the spring itself, since it was possible that it was at some point in late autumn or early winter that the animal and its parasite came into the required state of immunological equilibrium. A considerable amount of work was being done in Cambridge on the examination of mucosa at various periods of the year, and it would be interesting if the author would state what stage had been reached in that research.

Secondly, to examine a point upon which there was considerable difference of opinion in present times, he desired to refer for a moment to the significance of serum antibody in gastro-intestinal parasitism. It was unfortunate that most of the critical work on parasitic immunity had been done upon parasites which had a migratory larval phase—*Nippostrongylus muris*, the hook worms, *Trichinella spiralis* and lung worms, because in considering the great mass of gastro-intestinal parasites of the herbivores, there was a tendency to think of them in the same terms, whereas they differed in the fundamental respect that their larval phase was non-migratory so that, in a sense, they developed on one of the surfaces of the body rather than within the body itself.

Some of their secretions and excretions would be absorbed, since they lay deep in the crypts of an absorptive surface and, as was known, antibody developed as a result of their presence; but whether that antibody was functional was still questionable.

With the migratory parasite, passive and active immunity had been demonstrated with most of them and, of course, the work of Thorson with the secretions and excretions of the larvae of Nippostrongylus had shown that it was possible to absorb out the protective effect of immune serum, and so he had shown that in parasitism by migratory larvae, circulating antibody had an active function.

So far as Dr. Dunn was concerned, however, the protective character of circulating antibody in gastro-intestinal parasitism was still very much a matter for debate. At the moment in his view it could safely be regarded only as a useful indicator of the presence of larvae.

He suggested to the author the possibility of local resistance factors in gastro-intestinal parasitism. Local antibody had been demonstrated in a great variety of conditions—in poliomyelitis in the nasopharynx and faeces, in the faeces in cholera in guinea-pigs by Burrows and his coworkers in Chicago; and, of course, much nearer home by Kerr, Robertson and Pierce in another branch of parasitology —with Trichomonas. Kerr and Robertson appeared to have shown, in fact, that the uterus could be treated immunologically as a separate organism; or perhaps it would be more correct to say the surface of the uterus. Dr. Dunn suggested that the gut surface might be found to behave immunologically in a different way from the general tissues in helminth parasitism by non-invasive larvae. Certainly in gastro-intestinal parasitism, using the crude antigens at present available, there was still a great distance to go to explain many of the immunological processes which were taking place. At any rate, it was clear from the immense complexity and variety of the subject that one could not, with safety, consider one group of parasites as behaving immunologically in a similar way to another.

It appeared that one of the author's main achievements in his paper was to compel the reassessment of a great many of our previously accepted concepts in parasitic immunology. It was essential, with a varied subject such as the one under discussion, not to lose sight of the ultimate and practical object, the prevention of parasitic infestation. It was quite clearly the duty of those present, by general discussion, to try to bridge the gap between the considerable amount of fundamental information which was now available, and the practical application of that information in the veterinary field.

Mr. K. B. Sinclair, who also opened the discussion, said that as there was very little which could be criticised in the paper, his contribution would take the form of one or two additional remarks together with some findings from work done at Aberystwyth.

As with bacteria and viruses, the mechanism of acquired immunity to other parasites was believed to be dependent upon humoral and cellular forces or a combination of both. The concept of humoral immunity to bacteria and viruses had been universally accepted for many years, but only recently had that mechanism been shown to protect the host against invasion by protozoal and helminth parasites. On general principles one would expect that those parasites, having the most intimate contact with the reticulo-endothelial system would induce the greatest response. That, in fact, seemed to be the case, for most parasites living in close contact with the tissues of the host induced a good immunity. It was when parasites such as the ectoparasites and the gastro-intestinal nematodes were considered, which had comparatively little contact with the tissues of the host, that the picture was not so clear.

There was an interesting similarity between the hypersensitivity shown by Stewart (1955) to occur in the abomasum of sensitised sheep experimentally infected with nematode larvae and the hypersensitivity developing in the skin of horses and cattle exposed to the bites of arthropods shown by Riek (1954 & 1956). The latter found that a hypersensitivity associated with the release of histamine developed in the skin of horses exposed to the bites of sand flies, and cattle exposed to feeding ticks. The mechanism of both those phenomena was probably an antigen antibody reaction, the antibody being fixed in certain cells. Gordon (1950) found a sensitising substance to be present in the salivary glands of the arthropods he had examined, and it seemed as though that was yet another example of the antigenic properties of the so-called metabolic products. Some of the skin conditions seen in pigs and small animals might be a manifestation of that immune response.

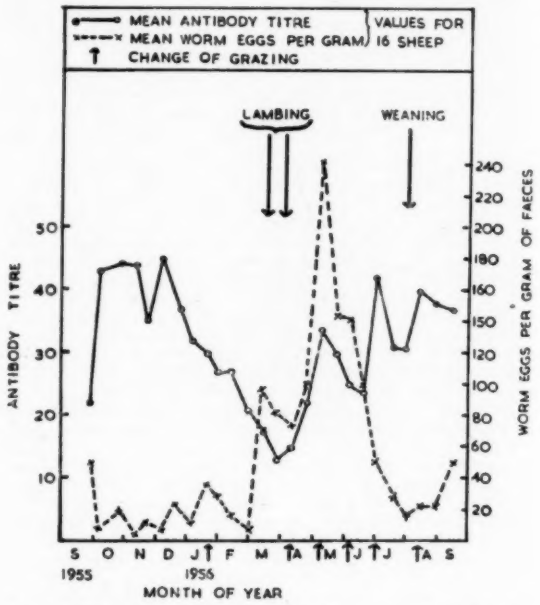

FIG. 1.—The mean antibody titre and mean number of worm eggs per gramme of faeces in a group of 16 sheep during pregnancy and lactation.

To consider the work done on sheep at Aberystwyth, Fig. 1 showed the mean antibody titre and the mean worm egg count in a group of 16 sheep. Attention was drawn to the decline in antibody titre during the late winter followed by a further depression at or about lambing. By electrophoresis it was shown that the antibody being measured formed part of the gamma-globulin fraction and the depression of antibody about lambing seemed to correspond to a reduction of gamma-globulin which occurred about that time. The antibody titre rose about 4 weeks after lambing, and it had been found to rise even in ewes which were housed before lambing and subsequently kept under worm-free conditions. It could be seen from Fig. 1 that from May onwards each change of pasture was followed by a fall in antibody level, and evidence suggested that the antibody titre reflected larval intake or development. Since the rise in titre in May occurred in sheep housed prior to lambing in April, it suggested that some larvae probably lying dormant began to develop at about that time and possibly contributed to the spring rise phenomenon.

Fig. 2 showed a similar series of records from lambs. It had been found that like other antibodies, the anti-nematode antibody was passively transferred to the lamb in the colostrum. The serum titre appearing in new-born lambs varied considerably, but was usually less in twins. It had been found that colostral antibodies were present in lambs for about 10 to 12 weeks. Active immunity began at about 16 weeks and that was followed by a gradual rise in titre until December, when the autumn rise in worm-egg output was declining. It might be seen from the graph that like the ewes, the antibody titre of the lambs tended to fall following changes of pasture.

Efforts had been made to try to discover any relationship between colostrum-derived antibody in the lamb and worm-egg output, and between level of antibody and resistance of lambs to infection with Nematode larvae. The findings as far as they went suggested that colostral antibody was not important in protecting the young lamb from infestation by nematodes, and there had been failure to show a

FIG. 2

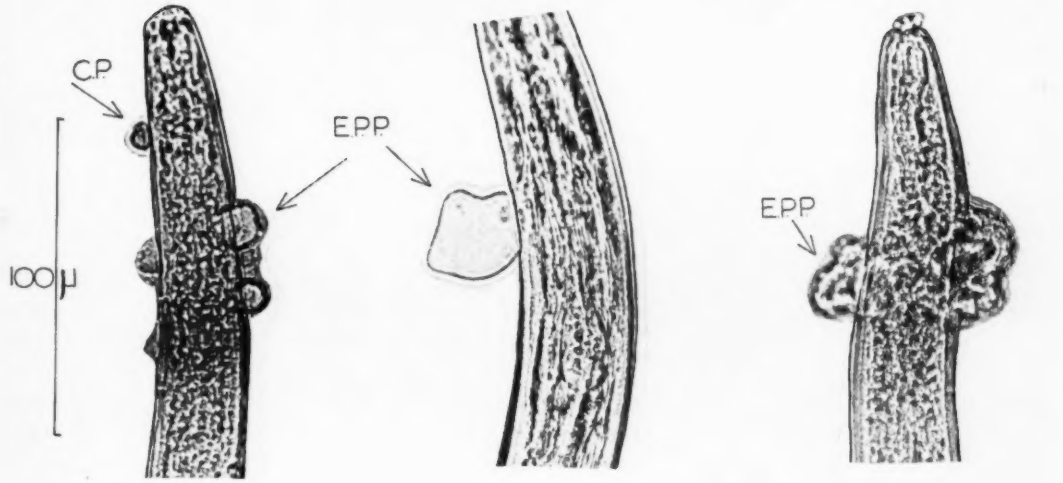

FIG. 2.—Third stage *A. lumbricoides* larvae after immersion in immune serum. O.P. = Oral Precipitate. E.P.P. = Excretory Pore Precipitate. C.P. = Cuticular Precipitate.

FIG 3.

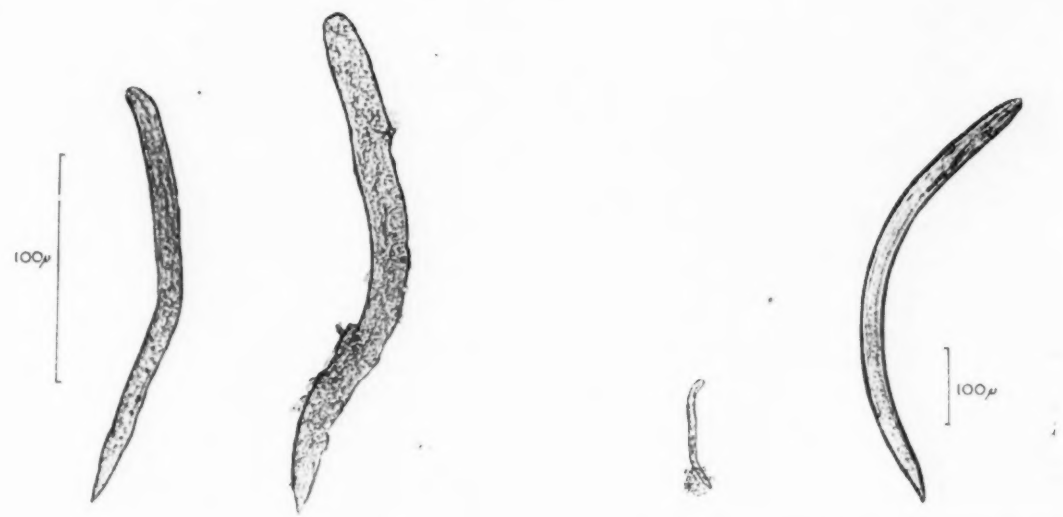

FIG. 3.—Comparison of *A. lumbricoides* larvae from immune (B & C) and normal (A & D) guinea-pigs. Note the marked reduction in size in the larvae from immune guinea-pigs and the internal disintegration especially in B.

FIG. 4.

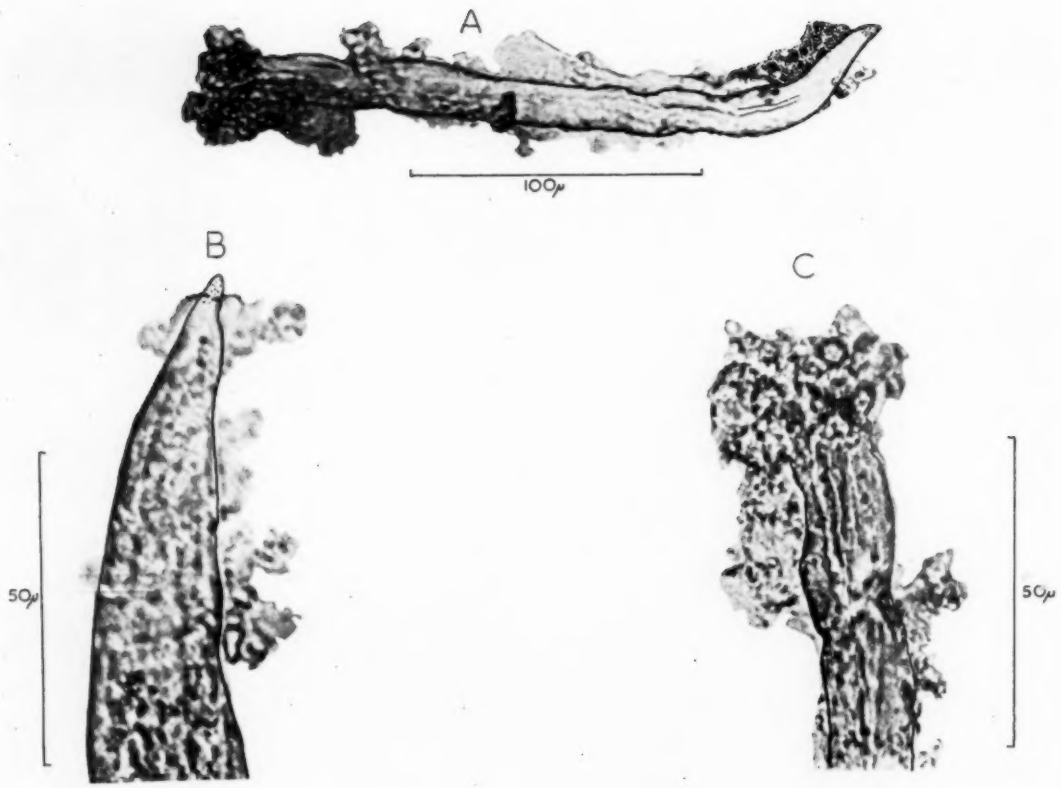

FIG. 4.—*A. lumbricoides* larvae recovered from immune guinea-pigs six days after infection. Note the marked degeneration in A; precipitates and cellular clusters in B and C.

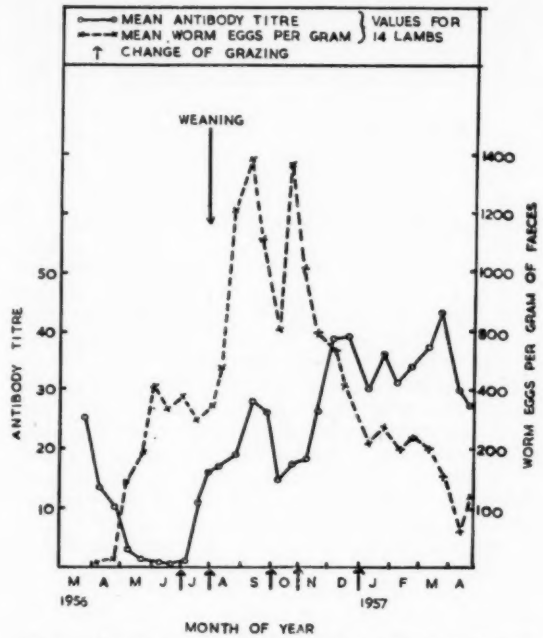

FIG. 2.—The mean antibody titre and the mean number of worm eggs per gramme of faeces in a group of 14 lambs during the first year of life.

relationship between antibody level and worm-egg output in young lambs. However, it appeared that the milking capacity of the ewe had a considerable part to play in protecting the young lamb from infection with gastro-intestinal nematodes. Whether that action was purely a question of a plentiful supply of food and therefore the lamb grazed less, or the milk acted in some other way, remained to be discovered.

Care must be exercised in drawing conclusions from studies of antibody levels as there was still much to be learnt about the basic immune phenomenon. Under normal conditions farm animals seemed to have been endowed by Nature with adequate defences against parasites. It was under the "improved" conditions of modern husbandry that the mechanisms seemed to be heavily taxed. Much more information was needed not only on the mechanisms of immunity as indicated by the author, but also on the factors causing breakdowns such as nutrition and stress. One line of approach had already come to light, for it had recently been shown by Nicol and his co-workers (1957) that hormones might have pronounced effects on the functioning of the reticulo-endothelial system.

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The General Discussion

R. N. T. W. Fiennes, Zoological Society of London. The larval retardation appears to be analagous to the condition encountered in the case of cattle kept under antrycide prophylaxis in tsetse-fly country. It was found that, whereas the drug weakened the protozoa, systemic invasion was prevented by antibody and the parasites were confined in a dormant state to such sites as the bone marrow and the cardiac capillaries. In this case, too, the effect of the antibodies could be damped down by exposure to unfavourable conditions of nutrition and stress; such was achieved experimentally by administering attenuated rinderpest goat virus or by provocation with such agents as TAB vaccine and adrenaline.

It appeared possible that some similar mechanism might be at work in the case of viruses in "carrier" animals and man; infectious hepatitis. Shope's work on swine influenza seemed to indicate this.

Dr. A. Foggie (Edinburgh). "In an attempt to keep them free from ticks for the first few weeks of life, groups of lambs were smeared with insecticides at birth and dipped two weeks later. Periodic tick counts were made on the treated lambs and on untreated control lambs running on the same pastures. For the first two or three weeks the counts of ticks on the treated lambs were significantly lower than those on the untreated lambs but by the fifth or sixth week this position was reversed and the untreated lambs carried a significantly smaller number of ticks than the treated lambs. This finding suggested that the untreated lambs had acquired a degree of immunity to tick-bite which was not possessed by the lambs which had been protected by treatment. I would like to ask Dr. Soulsby if this type of cutaneous immunity to external parasites is of common occurrence."

The Reply

Dr. Soulsby, in reply, referred to the question of the "spring rise" and said it was to be regretted that the person who was responsible for doing most of the work in this country on the subject, Dr. Morgan, had not contributed to the discussion. Dr. Dunn had dealt with a flock in circumstances where, during the winter time, the young would suffer very severe malnutrition with loss of weight and condition. On the other hand, as Mr. Sinclair had pointed out, the phenomenon of the "spring rise" had also been studied in flocks of sheep under conditions which were not applicable to Scotland. In fact the sheep which the author had dealt with gained weight during the winter, and despite this the "spring rise" occurred.

Mr. Sinclair had shown that there was a gradual decline of antibody titres in late winter, this being followed by the "spring rise"; the author had found the same thing. In his view the initiation of the "spring rise" was due to a progressive lowering of the immune status of the animals, and at some point there was either a large-scale invasion from the pasture by new larvae, or larvae which had been dormant in the mucosa suddenly became active and initiated the "spring rise." In his opinion nutrition, stress and all the other factors tended to modify the time when it occurred, but the basic phenomenon which allowed the "spring rise" to occur was a progressive decrease in immune status.

In reply to Dr. Dunn regarding his query about hibernating larvae the author was unable to find such larvae in the mucosa of sheep examined during the winter and spring at Cambridge. Dr. Dunn also referred to the gastro-intestinal parasites as being virtually outside the body. The author did not agree, for although, perhaps, they were strictly speaking outside the body, there was good evidence that the depths of the intestinal crypts were sites where there was a good movement of body fluids and cells to and from the tissues. Hence, physiologically speaking, such sites might be regarded as being virtually inside the body.

Mr. Sinclair's opening was very interesting in that he had confirmed the author's observation to a very great extent.

Dr. Foggie had made an interesting observation on the subject of ticks and immunity to them. Immunity to ticks had been demonstrated in guinea-pigs; this immunity reached its peak in 14 days and was associated with antibody which could be passively transferred. Probably the first person in this country to do work in connexion with immunity to parasites was Professor Gordon, of Liverpool, who worked with insect larvae.

In reply to Dr. Howell's query the author said that passive transfer of immunity had been demonstrated in many cases.

Dr. Soulsby said that he would be very chary about giving any explanation of the point raised by Mr. Fiennes. It was dangerous to generalise without any definite information.

The General Examination of the Bull for Soundness with Special Reference to the Assessment of Fertility

BY

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Preamble

THE Concise Oxford Dictionary defines "sound" as meaning "healthy, not diseased nor injured nor rotten" so that "soundness" can be taken as the state of being healthy, not diseased nor injured nor rotten. In the present context however such a definition is inadequate, for in dealing with soundness in animals we are concerned with their suitability for the purpose which they are intended to fulfil. In the bull this purpose is a simple one, it is that he should get cows into calf, that he should continue to get cows into calf and that in doing so he should cause no injury to those cows either by mechanical damage or by transmitting pathogenic organisms.

For the purpose of this paper we will consider only the bull to be used by natural mating. The case of the insemination bull is in many respects entirely different and in some ways the problems involved are more simple. There are bulls which are eminently satisfactory for use in an insemination centre which would be useless for natural mating and the converse is also certainly true.

The spread of artificial insemination has given great impetus to studies on the examination of the bull and the assessment of fertility from semen tests. As will be seen later, in considering this aspect of soundness, we have to draw on the results of work done almost exclusively with insemination bulls but it would be wrong and perhaps misleading to apply results so obtained to natural mating bulls unreservedly.

In order to get cows into calf the bull must be willing to serve and this implies that he will serve within a reasonable time, although again the particular purpose for which he is used will influence one's impression as to what is reasonable. A bull which is running with the cows can be extremely slow without this being of any great moment whereas if used by hand service, particularly in these days of high labour costs, extreme slowness will be a major disadvantage.

Being willing to serve, the bull must then be capable of mounting, and for this it is clear that there must be no gross abnormality of the hind limbs and feet, nor of the back. Willingness and ability to mount can best be measured by providing the opportunity and watching the performance.

Having mounted, then the bull must be capable of intromission. Curvature (Milne, 1954) and inability to protrude the penis sufficiently are the most common causes of failure to achieve intromission. I have seen three cases of curvature in Ayrshire bulls and in each case the curvature has been downward so that the glans penis made contact with the cow 2 or 3 inches below the ventral commissure of the vulva. In one case the owner had attempted to improve matters by digging a hole in which the cow could stand but, as might be expected, this had proved useless. Each of these three bulls was eager to serve and each one worked well into an artificial vagina.

It has been suggested that inability to protrude the penis sufficiently might be due to shortness of that organ, to congenital shortness of the retractor penis muscle, to the development of adhesions between the penile and preputial epithelium (Arthur, 1956) or to phimosis resulting from constriction of the preputial orifice. I have seen several young bulls in which there appeared to be a true shortness of the penis but in each case normal service was possible after a week or two of unsuccessful attempts and in these bulls the eventual penile protrusion was of normal length. Apart from these cases, which were probably only manifestations of immaturity, I have seen none in which I could suspect a shortness of either the penis or the retractor penis muscle. Milne (1954), records neoplasia of the penis as a cause of phimosis but in my experience it is much more commonly a cause of paraphimosis.

Failure of ejaculation in the bull, once intromission has been achieved, is very rare. This is probably in large measure due to the extreme briefness of the bovine copulatory act, intromission and ejaculation occurring almost simultaneously.

The ejaculate must contain a sufficient number of normal spermatozoa, contained in a suitable substrate, to ensure the fertilisation of any normal ovum with which they come into contact and this fertilisation must lead to the production of a zygote which is capable, given satisfactory intra-uterine conditions, of developing into a normal full term calf. A suitable substrate presupposes that, in addition to being a suitable medium for sperm survival, it contains no pathogenic or potentially pathogenic organisms.

Having, in this preamble, decided on the functions which we require a bull to perform we can consider how, in any given bull, to attempt to measure that he is in fact capable of performing them. At the outset let it be said that the test of fertility, in all its aspects, is whether the bull does in fact get cows into calf and those cows carry their calves to full term. If a bull fulfils these criteria then, however bad his semen as shown by laboratory tests, he is still fertile.

Our examination of the bull is at best an inferior substitute for the critical test of actual breeding performance.

Examination of the Bull

Collection and examination of a series of semen samples is clearly an essential part of our examination.

In my view the difficulties of obtaining a truly representative sample have never been stressed sufficiently. There can be few, if any, other materials in veterinary medicine which are regularly used for laboratory tests and in which the collection depends entirely on the active co-operation of the animal concerned. Our interests are not really with the sample of semen a bull will give when ejaculating into an artificial vagina but with the sample he will deposit into the vagina of an animal which he mates naturally. We must so arrange our collection techniques that semen produced in either circumstance is as nearly as possible the same.

In the course of studies on the effect of nutrition on the semen production of bulls it was necessary, before attempting to influence semen quality adversely, to maintain each bull on a control ration for some considerable time. During this time regular semen collections were made and it was found that the slightest deviation from a standard collection technique would lead to a fall in semen quality shown most commonly by a marked fall in sperm count, motility and viability. These were bulls well used to artificial collection and the deviations in technique and circumstance were of the most minor character, a different teaser cow, disturbance from a passing vehicle, etc. How much more extreme is the difference between artificial collection by a complete stranger and natural mating in a well known environment. Blom (1950) and Hignett, S. L. (1951) have each recorded the effect of transportation upon the semen quality of bulls and it is unfortunate that many of the animals which we are asked to examine have been moved from one farm to another a few days previously. Any tendency for service behaviour and semen quality to be depressed by the circumstances of our collection is accentuated in the case of bulls which are, in any case, slow to serve. This does present grave difficulties in the case of beef bulls.

In order then that there shall be as little disturbance of the bull as possible, collection of semen should be the first part of the examination to be carried out. Although necessary, this is inconvenient since, in the writer's view, no delay is permissible between semen collection and the carrying out of the preliminary stages of the examination. In practice it means that further inspection of the bull must be delayed until the semen has been dealt with.

As the bull is led out for service note can be taken of his gait ; it will be seen whether he moves freely or whether there is any sign of stiffness or lameness. The eagerness and ease with which he mounts will also be noted although due allowance must be made for age. Once the bull has mounted there must be no undue haste in making the collection. No fear need be entertained that if collection is too long delayed the bull will dismount. This might happen, but if a bull is keen enough to mount once he will mount a second time. The delay whilst waiting for the penis to develop full turgidity should be used to examine it visually, looking particularly for neoplasms, ulceration and haemorrhages, noting if the protruded length is normal and, so far as possible, deciding if there is any marked curvature. In cases of curvature of the penis there will be a history of inability to serve and this is best checked by permitting an attempted natural mating.

Immediately after collection the tube containing the semen is placed in a vessel holding water at 30° to 35° C. and a sample withdrawn for a subjective estimation of motility. This estimation must be made immediately ; before the next ejaculate is collected. Due precautions will of course have been taken against temperature shock and against damage due to contact with harmful substances such as water.

Most workers consider that, in order to make a satisfactory examination, three ejaculates should be collected. Whilst agreeing with this view it is my practice to make the final assessment on the best ejaculate. Without having any definite proof—and in fact such proof would be most difficult to gather—it seems at least unlikely that the bull will ever give better semen by artificial collection than he will by natural mating.

As soon as all the collections have been made and all the motility estimations carried out, smears for morphological examination should be prepared. For all general purposes the nigrosin-eosin method of Hancock (1951) is satisfactory both for an estimation of the proportion of supra-vitally staining, and therefore dead, sperms, and also for a not too precise but generally useful morphological examination. In staining semen for an estimation of the live/dead ratio great care must be taken against causing temperature shock by ensuring that semen, stain and all glassware used are at the same temperature (Hancock, 1951, Bishop *et al.*, 1954). Even under farm conditions this is not an insuperable difficulty as the glassware can easily be warmed by being placed in the lumen of a spare, and warm-water-filled, artificial vagina. The main disadvantage of this stain is that its use might cause a proportion of sperms to develop a curvature of the mid-piece (Bishop *et al.*, 1954), and that it does not always show clearly the acrosomal abnormality (Teunissen, 1946, Hancock, 1949, 1953) which is associated with sterility in some Friesian bulls. These disadvantages can, under farm conditions, best be overcome by preparing duplicate smears stained with indian ink.

Much more complex staining techniques are of course in common laboratory use but in the writer's opinion the disadvantage of preparing smears from material which has been transported to a laboratory, perhaps having spent the night in the post, far outweigh any possible advantage from an improved stain.

After the preparation of smears suitable dilutions in formol-saline should be made for a subsequent sperm count, a small part of the semen should be placed into a sterile vial for later bacteriological examination and the remainder should be diluted with previously prepared egg-yolk citrate or egg-yolk phosphate buffer a note being made of the degree of the dilution (suggested 1 : 4). The tubes containing this diluted semen being then well wrapped in numerous thicknesses of newspaper and placed in a vacuum jar with ice. This diluted semen can, on arrival at the laboratory, be used for certain of the more simple metabolic and viability tests.

The above is probably the minimum which should be carried out on the farm and even then it must be realised that the material reaching the laboratory will be unsuitable for certain tests, *e.g.*, estimation of fructolysis index.

Having completed the first stage of semen examination the bull should be submitted to a careful clinical examination. The scrotum, cord, testes and epididymis are palpated carefully and the seminal vesicles, ampullae and posterior parts of the vasa deferentia are examined *per rectum*. In Britain the most commonly found abnormalities are testicular hypoplasia (Arthur, 1956), epididymitis and seminal vesiculitis. Blom & Christensen (1947) reported on the variability of the positioning of the ampullae in relation to the seminal vesicle, this was confirmed by Bishop *et al.* (1954) and has also been my experience.

In the preamble it was stated that in addition to being able to serve a cow and giving potentially fertile semen the bull must also not transmit any pathogenic organisms.

Although a very large number of pathogenic and potentially pathogenic organisms have been recovered from bull semen our greatest concern, in the present context, is with *C. pyogenes*, *Br. abortus*, *Tr. foetus*, and *V. fetus*.

Hancock and Kelly (1948) showed that many clinically normal bulls excrete *C. pyogenes* in the semen. This excretion is not invariably associated with either infertility or with genital disease in the female but, nevertheless, such a bull should be regarded with suspicion.

Brucellosis, trichomoniasis and vibriosis present many difficulties largely due to the virtual impossibility of proving a negative diagnosis. In making our investigation the history of the bull can be of great assistance but the reliance to be placed on any statement must, to a large extent, depend on one's own judgment. In general it can be said that an assurance that the bull has never served must always be regarded with scepticism.

Br. abortus can best be detected by culture of semen and agglutination tests of blood serum and seminal plasma.

Examination of preputial washings is the commonest method of examining for *Tr. foetus* although the writer prefers the method of Bartlett (1949). By this technique a portion of undiluted preputial fluid is collected with a pipette.

At the present time we are most likely to be concerned with possible infection with *V. fetus*. Not only is this organism one of the most important and widespread causes of infertility but its detection in the bull is singularly difficult. As has been shown repeatedly, cultural examination of semen, even from infected bulls, is most unlikely to yield the organism and our only means of arriving at a clear diagnosis is by making use of a biological test. Edgson & Scarnell (1955) used as a criterion of freedom from infection test mating of from 5 to 10 heifers all of which after a period of three months gave negative vaginal mucus agglutination tests. This would seem to be a satisfactory standard but is extravagant both of heifers and of time. To overcome these disadvantages Adler (1952, 1956) introduced a test in which only one heifer is used for each bull and from which vaginal and uterine material is cultured twice weekly for three weeks. Adler found that six negative cultural examinations were sufficient to assume freedom from infection in the bull and these results have been confirmed by Morgan (1956, 1957) and by the writer. Although this technique appears to give reliable results it is very costly and there is not as yet, nor is there great likelihood of there being in the near future, any institute which can undertake this work for the general run of bulls. The widespread biological testing of bulls must wait upon the development of methods using cheap laboratory animals. Although success in this respect has been claimed by Adler (1953), Power (1954) and Robinson *et al.* (1956) all British workers have so far failed to infect small laboratory animals with *V. fetus* infected semen. This has been our own finding with guinea-pigs ; it has also been that of Morgan (1956).

That the bull should be free from any intercurrent disease, quite apart from those which have a particular reproductive significance, is obvious and where there is the slightest doubt on this point he should next be submitted to a complete clinical examination.

The Semen Tests and Their Interpretation

Although only one section of the examination of the bull for soundness, semen tests are a most important part and present problems not encountered in the other parts of our examination. In general their performance presents no great technical difficulties nor, except in a few instances, do they call for any complex equipment. Everything needed for quite a wide range of examinations can be found in the ordinary moderately well equipped surgery. The problems arise from the nature of the material under test and the extreme difficulties of interpretation.

The difficulties in the nature of the material arise, as has already been stated, from the difficulty of obtaining a representative sample and from the extreme fragility of that sample once obtained. Semen, particularly when undiluted, can be damaged so easily that few of us can feel happy about examining specimens from the field unless we know the capabilities of the collector very well indeed.

The needs of insemination centres have led to intensive research into semen tests and their correlation with fertility and although we must learn what we can from such work it helps us surprisingly little in our present problem. The requirement in a centre is rather to choose between samples than between bulls, and in most investigations the bulls have been of "normal" fertility although of varying efficiency within the normal range. Can we necessarily assume that a test, even if such existed, which would accurately predict the conception rate of a semen sample, when used after dilution and storage for artificial insemination, would also accurately predict its fertilising power by natural mating ? Although limitations of space do not allow the subject to be discussed in great detail it is perhaps profitable to consider some of the more commonly used semen tests and to see what evidence there is that these give any indication of fertility. This subject has been exhaustively reviewed by Anderson (1952).

Motility

Estimation of motility is, under farm conditions, invariably subjective. A drop of semen is placed on a

warm slide, and examined under the low power of the microscope. Points are awarded for wave motion and motility according to the individual's favourite scoring system. The introduction of the comparing chamber by Blom (1946) has made this examination much easier and by using it the difference between semen of good and semen of poor motility can be appreciated more readily. There is no doubt that in the hands of an experienced worker this subjective estimate will give highly reproducible results (Rothschild, 1950) but it is not possible to compare results obtained by different workers. To overcome this disadvantage objective methods have been developed by Rothschild (1949) and by Bosselaar & Spronk (1952). Rothschild measured the frequency of the change of impedance in fresh semen by passing through it an electric current between platinum electrodes. In Bosselaar & Spronk's method a magnified image of the semen is thrown on to a screen in which there is an aperture. Each time the image of a sperm crosses the aperture it actuates an electrical counting system.

Sperm Count

The concentration of sperms in an ejaculate is clearly of importance but the accurate estimation of this concentration is by no means always simple. The obvious method is by the use of a haemocytometer and this is undoubtedly the most accurate technique in the hands of a skilled technician, but very great care is necessary if reproducible results are to be obtained. Fresh semen is not homogeneous so that there is a possibility of a grave sampling error and the shape of bovine spermatozoa tends to make them difficult to disperse evenly in the diluting fluid. Bane (1952) records that the sampling error alone might amount to 55 per cent. unless steps are taken to homogenise the semen. Clearly such homogenisation will have an effect on the semen which must influence the results of other tests. Haemocytometer counts if performed on a sufficient number of replicates to give high accuracy, are also extremely time-consuming. Numerous attempts have been made to introduce methods which are speedy and accurate and at the same time call for somewhat less skill. Of these the most widely used are the comparison with opacity tubes (Salisbury *et al.*, 1943) and the measurement of light transmission, through a suitably diluted sample, by means of an absorptiometer (Willett & Buckner, 1951).

Whilst appreciating that a true count can only be made with a haemocytometer it is my view that for general field use the opacity tubes have much to recommend them. They can be used quickly and easily and I have found that after a little practice most technicians can obtain reproducible results which are within 10 per cent. of haemocytometer counts. It is at least debatable whether greater accuracy than this would serve any useful purpose in the examination of infertile bulls. When the semen contains much suspended matter, other than spermatozoa, this accuracy will not, of course, be reached but the presence of this matter will be detected when the stained smears are examined and due allowance can then be made. Details of the technique of making a haemocytometer count and of using the opacity tubes are given in B.V.A. publication No. 22 (1953).

Estimation of Percentage Dead Sperms

When making the initial estimation of motility some impression will be gained of the approximate proportion of immotile sperms, for although motion will be imparted to them by the active sperms they show as dark specks of "drift-wood" as compared with the highly translucent live sperms. One's impression is that this difference in appearance is due to the fact that whereas the live sperms move swiftly in and out of focus the dead ones tend to remain in view for very much longer. More accurate and objective methods of counting the number of dead or immotile sperms have been developed. Bane (1952) gives details of a technique in which semen is diluted with a physiological diluent and then, by means of a haemocytometer, the non-motile sperms are counted. After freezing and thawing —which will kill all the sperms—a total count is made and from these results the percentage immotile is calculated. In this paper Bane stresses the overriding importance of using a suitable diluent and of maintaining a careful temperature control throughout the counting. It would seem that this method is not suited to field use. Undoubtedly the best method for general purpose is to make use of the properties of eosin in staining dead spermatozoa and leaving live ones unstained (Lasley *et al.*, 1942, Shaffer & Almquist, 1948, Mayer *et al.*, 1951, Hancock, 1951, Campbell *et al.*, 1953). Unless the staining is carried out with care (Hancock, 1951) grossly inaccurate results will be obtained, in fact Bishop *et. al.* (1954) used a modification of the method as a means of measuring resistance to temperature shock. Nevertheless the author has found no difficulty in carrying out the methods on the farm, and recommends it for general use.

Morphology

Although smears should be prepared at the earliest opportunity after collection, examination of these smears can be delayed until circumstances are convenient. Under oil-immersion from 100 to 300 spermatozoa are counted and the numbers and types of abnormalities recorded.

Viability

In insemination work it is obviously necessary that spermatozoa should remain viable for as long as possible. Under uniform conditions of dilution and storage samples retain their motility for varying periods and it has been suggested that there might be a correlation between persistence of motility and fertility. Most workers have measured persistence of viability in semen diluted with the usual egg-yolk citrate or egg-yolk phosphate diluents and held in a refrigerator at temperatures approximating to 5° C. (Margolin *et al.*, 1943). This has become known as the low temperature viability test. Beck & Salisbury (1943) found that there was a good correlation between persistence of motility at 5° C. and persistence at 46·5° C. and so suggested using viability at the higher temperature, the high temperature viability test, as a rapid means of estimating fertility. Although giving a result in a few hours as compared with several weeks in the case of the low temperature viability test the necessity for a water bath renders the high temperature viability test difficult to use in the field.

Methylene-Blue Reduction Time

In the presence of live spermatozoa methylene blue takes up two atoms of hydrogen, and is converted into a colourless compound. The rate of decolorisation of a standard methylene-blue solution is used as a test of semen quality (Sorenson, 1942, Beck & Salisbury, 1943, Van Demark *et al.*, 1945). Although it is necessary to hold the semen-methylene blue mixture at a constant temperature (various workers have used temperature ranging from 37° to 47° C.) the time taken for decolorisation is so brief, being under 15 minutes in the case of good samples, that a water bath can easily be improvised from a beaker and the temperature maintained by judicious addition of warm water.

Resazurin. Reduction Time

Semen will reduce resazurin, converting it first to pink and then to white. Erb & Ehlers (1950) suggested the use of the resazurin reduction time as a test of semen quality and Erb *et al.* (1952) described a modified technique. Although I have not used the test there seems no reason why it should not be performed under farm conditions.

pH.

Normal freshly ejaculated bull semen is slightly acid and on incubation the acidity increases, largely due to the accumulation of lactic acid arising from the metabolism of fructose. Both initial *p*H and the drop in *p*H on incubation can therefore be used as tests of semen quality (Reid *et al.*, 1948; Anderson, 1952).

Fructolysis

Mann (1946) was the first to show that the reducing carbohydrate of the seminal plasma was not, as had been thought, glucose but d(—) fructose produced by the seminal vesicles. In 1948 he suggested that initial fructose and the rate of fructolysis could be used as tests of semen quality. As a measure of the rate of fructolysis he proposed the fructolysis index which is the mg. fructose utilised by 10^9 spermatozoa in 1 hour at 37° C. Because of the technical difficulties this test is suitable only for the specialist worker.

In addition to the above, numerous other semen tests *e.g.*, O_2 uptake and hyaluronidase content have been proposed but generally these are not practicable under field conditions.

Correlations With Fertility

For any test or combination of tests to be of value it must be possible to correlate the results obtained with the fertility of the semen tested. For obvious reasons most attempts at obtaining such correlations have been made with semen used in insemination work and the voluminous literature which has resulted is remarkable chiefly for its lack of unanimity. Certainly it can be said that at the present time no ideal series of tests can be recommended nor is there a clearly defined boundary between fertile and infertile semen. Summarisation of the literature is made more difficult by the variations in the techniques of the tests as used by different workers, and even where there is a statistically significant correlation between a test, or a series of tests, and fertility, this correlation is often too low for the test to be of great practical use.

Despite the fact that the estimation of initial motility is perhaps the most widely used of all measures of semen quality and that many experienced workers in the field place great reliance on it (for instance Melrose (1952) says: "At this Centre the experience has been that the assessment of initial motility of semen at the time of collection is, in spite of its shortcomings, the most reliable practical method available to date") there is little supporting experimental evidence. This is undoubtedly due to the fact that, in those investigations which have been carried out on semen used in routine artificial insemination, the samples tested and used have themselves been selected on the basis of initial motility. However, Swanson & Herman (1944), Lasley (1951), and Bratton *et al.* (1956) found a positive correlation between fertility and the percentage of motile sperms and Bishop *et al.* (1954) found a similar correlation between fertility and impedance change frequency. Herman & Swanson (1941), Erb *et al.* (1950) Buckner & Willett (1950), Branton *et al.* (1951), Cupps *et al.* (1953), and Buckner *et al.* (1954) all failed to show a clear relationship with fertility.

Willett (1950) and Bratton *et al.* (1954) have shown that a satisfactory conception rate can be obtained from the insemination of from 6 to 10,000,000 spermatozoa so it is clear that by natural service there will be an absolute deficiency only in cases of extreme oligospermia. Nevertheless many workers are agreed that semen which contains less than 500,000 sperms per $mm.^3$ is unlikely to be of high fertility (Johnston *et al.* (1951), Branton *et al.* (1953)). One assumes that a low sperm count is of importance in indicating defective spermatogenesis. As with initial motility nearly all those who have used insemination material have failed to demonstrate a correlation with fertility. Bishop *et al.* (1954) and Bratten *et al.* (1956) are exceptions.

Madden *et al.* (1947), Erb *et al.* (1950), Bishop *et al.* (1954) and Bratton *et al.* (1956) all found a good inverse relationship between the percentage of sperms staining with eosin, and fertility, whereas Cupps *et al.* (1953) did not.

It is in considering the significance of morphologically abnormal sperm that our difficulties in interpretation reach a peak. A few specific abnormalities such as the defective acrosome in some Friesian bulls (Teunissen, 1946, Hancock, 1949, 1953) are of clear-cut importance but the significance to be attached to other abnormals is not by any means clear. All samples of semen contain some abnormals and the problem is then to decide at what level these abnormals become important and also to determine whether all the commonly found abnormals are of equal significance. Again, nearly all those working with insemination material are unanimous in finding no relationship between the percentage of abnormals and conception rate. In view of their highly selected material this is not surprising. Probably in order to facilitate mathematical calculations most of these workers have not differentiated between types of abnormals.

Rollinson (1951) made an exhaustive study on 29 infertile or sterile bulls and 14 fertile bulls all of which were used by natural mating. He found a higher proportion of abnormal sperms in the moderately

fertile bulls than in the normal bulls but the low fertile and sterile bulls tended to have less abnormals than the moderately fertile. In agreement with many earlier writers he considers head and mid-piece abnormalities to be of greatest importance with abnormalities of the tail of less account. He suggests that bulls giving semen with about 7 to 5 per cent. deformed heads, 5 per cent. tailless sperms, 15 per cent. deformed mid-piece and 1 per cent. abnormal tails are likely to give fertility of about 40 to 60 per cent., and states that below this level prediction is of little use. I am in general agreement with this view but would stress that no rigid standard can be laid down. I well recall the case of a beef shorthorn bull which on repeated sampling over a period of some months consistently gave semen with 40 per cent. pyriform heads and yet was of the highest fertility.

Several groups of workers have found viability at low temperatures a good guide to fertility (Herman & Swanson, 1941, Margolin *et al.*, 1943, Swanson & Herman, 1944, Ludwick *et al.*, 1948, Erb *et al.*, 1950, and Bratton *et al.*, 1956) and contrary reports are few, although Buckner & Willett (1950), showed only a low correlation. In view of the simplicity of the test, in which every one of its many modifications is carried out, this comparative unanimity is heartening. Unfortunately the delay in obtaining a result is a major disadvantage. Although Beck & Salisbury (1943) obtained a very good correlation between high-temperature viability time and low-temperature viability time the high-temperature test has not proved a good indicator of fertility in my hands.

Buckner & Willett (1950), Branton *et al.* (1951), Buckner *et al.* (1954), and Bratton *et al.* (1956) all found methylene-blue reduction time to be correlated with fertility but in no case was the correlation coefficient high. Since most of these workers used a standard dilution of semen, rather than semen diluted to a standard concentration, the results obtained were to some extent governed by sperm concentration.

Erb & Ehlers (1950) Erb *et al.* (1950, 1952) have shown good correlations between fertility and resazurin reduction time. The author has no experience of using this test but it would seem to have no particular advantage over the methylene-blue reduction time with which it has a close relationship.

Bratton *et al.* (1956) found that the initial *p*H of semen gave a highly significant, although low, correlation with fertility whereas Swanson & Herman (1944) found only a non-significant correlation. Herman & Swanson (1941) considered the initial *p*H to be a poor guide to the value of semen except that when the *p*H was over seven the sample was usually of very low viability. Blom (1950) found such a high *p*H to be associated with disease of the accessory glands.

Most workers have failed to find that the fructolysis test is of great value as a measure of fertilising power. The most notable exceptions are Hill & Gassner (1951), Gassner & Hill (1952), and Gassner, Hill & Sulzberger (1952). They found a good correlation and their results indicate that a rise of one in the fructolysis index is associated with a rise of 5·17 per cent. in the 60 to 90 day non-return rate. Melrose (1952) was unable to confirm these results and Bishop *et al.* (1954) found only a slight correlation with fertility.

Conclusions

It will be realised that any attempt to lay down minimum standards for semen is fraught with the gravest difficulties. Blom (1950) considered that semen with the following values, over 500,000 spermatozoa per mm.^{3}, initial motility 30 to 40 per cent. with distinct wave motion, methylene-blue reduction time under 25 minutes and primary abnormalities less than 15 per cent. should be of high fertility. If the concentration of spermatozoa is from 200,000 to 500,000 per mm.^{3}, 10 to 30 per cent. spermatozoa show progressive motility, there is no wave motion, the methylene-blue reduction time is from 25 to 35 minutes and there are 15 to 20 per cent. primary abnormalities the semen is of doubtful value.

Branton *et al.* (1951) suggest that suitable minimum standards for samples (not bulls) to be used in artificial insemination are a concentration of 500,000 per mm.^{3}, an initial progressive motility of at least 50 per cent. and a methylene-blue reduction time (by a technique different from that used by Blom) of under 9 minutes. However, Johnston *et al.* (1951) considered that although these criteria were generally suitable the percentage of spermatozoa showing initial motility should, for highest fertility, be somewhat greater than 50 per cent.

Rollinson's (1951) opinion, being based on bulls used for natural mating, carries particular weight in the present context. His criteria for morphology have already been given and to these he links for highest fertility a total ejaculate content of 2,500,000,000 sperms or more and an initial progressive motility of over 70 per cent.

The authors of B.V.A. handbook No. 22 (1953) suggest that the semen should show wave motion, have a sperm concentration of over 400,000 per mm.^{3}, have a methylene-blue reduction time of under 15 minutes, have less than 15 per cent. primary abnormalities and a low-temperature viability time of at least 10 days. My own opinion is that, in the absence of specific morphological findings which indicate sterility these criteria are about right for most dairy bulls as seen under British conditions. Although no supporting literature can be found, however, I hold the view that in many cases beef bulls used by natural mating will prove to be of high fertility even when giving semen which does not conform to these minimum standards. The isolated case of the bull with 40 per cent. primary abnormalities has already been mentioned but more commonly the deficiency is in concentration and motility. To what extent this is a true measure of the production of semen of apparently lower quality by beef bulls and to what extent it is merely a reflection of their lesser libido is uncertain.

It is perhaps in a degree heartening that most workers who have laid down criteria have confined themselves to the more simple tests. Where many tests have been investigated the conclusion has often been reached that, in the present state of our knowledge, there is little to be gained by a performance of the more complex tests. Bishop *et al.* (1954) state that the physical activity of bull semen is related to fertilising capacity and that this can be measured by the determination of the concentration of spermatozoa, by the determination of the incidence of dead spermatozoa, and by measurement of the impedance change frequency.

They continue " methylene-blue reduction, fructolysis and O_2 uptake add little to the information gained by the three tests mentioned above." As they themselves point out, their results were obtained from a selected sample of bulls, all of which were reasonably fertile.

I hope that the foregoing will have indicated to those who are not well acquainted with this work some of the limitations of our knowledge. Entirely because of this lack of knowledge, however, and for this reason alone, I feel that the only safe course in examining bulls in the field is to apply to them every test which is possible and then to admit that in many cases it will be impossible to give a clear-cut opinion. In few cases will it be desirable, or indeed possible, to form an opinion on the basis of laboratory tests alone. The laboratory worker can give guidance but it is only the clinician who is familiar with all aspects of the case who can arrive at the final diagnosis. Without doubt the ideal is for the clinician and the laboratory worker to be combined in the one person, for only then can all the information be weighed in the most efficient manner.

Summary

The meaning of " soundness " as applied to the bull is considered and the procedure to be adopted in examining a bull is briefly outlined. Particular stress is placed upon the difficulties of obtaining representative semen samples and the great care which must be exercised in this respect.

Certain of the more commonly used tests of semen quality are briefly discussed and the evidence for their value as predictors of fertility is also considered. In doing this no attempt has been made to review the literature exhaustively but merely to present, primarily to the non-specialist, those papers of greatest practical application.

The impracticability of applying results obtained with insemination bulls to semen from bulls used for natural mating is considered, but the previously suggested criteria for fertile semen seem to have proved generally satisfactory. The suggestion is made that, under British conditions, there should be two sets of criteria, one for dairy bulls and one for bulls of the beef breeds.

The paper is written primarily to give help and guidance to the non-specialist working on the farm.

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THE SPEAKER'S INTRODUCTION

Mr. Hignett, in introducing his paper, said he had found the writing of it a difficult task largely because he was endeavouring to write something which would be of direct help and of direct benefit, particularly to the non-specialist and to the practitioner who was the person so often called upon to examine bulls in the field. The man who saw and examined the bull on the farm was above all the person who should give an opinion as to whether a bull was likely to be of high fertility, or whether it was likely to be of low fertility. He desired to spread the idea that in his view the collection of a sample and the dispatch of that sample to some distant laboratory, and then the receipt by return of a nicely typed laboratory report, were a poor substitute for making a personal examination.

The question of bull examination had come to the fore recently in the veterinary world, and there was no doubt that very often the examination was performed in a way which could be improved upon; and again it was his aim to try to give some guidance on how he considered one should go about the job of examining the bull.

The performance of simple laboratory tests always seemed to strike terror into the hearts of many people. The tests which tended to prove useful were, on the whole, very simple. There was no difficulty in the performance of such tests. The difficulties were always in interpretation, and to begin to interpret tests without taking full account of clinical findings and the history of the particular case was, of course, quite impossible. At the same time, he had endeavoured to show what evidence there was for the validity of each one of the tests which had been commonly used. He desired to stress as much as possible that by and large many of the tests were not particularly good indicators of fertility, that evidence as to their efficiency was to a large extent lacking, and also that it was shown that much of the work had, of necessity, been done with insemination bulls with very special problems. Those factors tended largely to invalidate a great deal of the work in connexion with the natural mating bull.

So far as the non-specialist was concerned, the natural mating bull was his chief concern. At the same time, whilst desiring to stress the general lack of knowledge, in his opinion much more of that type of work could usefully be done. There was a largely untapped field at the moment with regard to bull examination which could be investigated, and if it were so investigated a very useful service to the farming community would be performed.

A point which was of paramount importance concerned collection technique. Semen was a very different material from other material collected from animals for examination. Its composition and quality could be altered so much by the details of the collection technique that unless a good technique was used, the remainder of the examination went for nothing. That had been brought forcibly to his mind when instructing students in the collection of semen. He had found that the semen they obtained was of much poorer quality than that which he himself obtained from the same bull. One tended to be so delighted, particularly with the slow bull, at having obtained a sample of semen, that it was sometimes overlooked that the sample was not as good as it might have been. To collect a sample of semen hurriedly, to dispatch it to the laboratory and to receive back a report on it were useless. It was a field above all others in which ideally the clinician and laboratory worker should join forces. As time progressed there would be a tendency to do more examinations of bull semen on the farm. He became more dissatisfied with the results obtained from material which had been stored even for a few hours. Of course, to carry out the type of investigation which he had outlined in the first part of the paper took some hours. It would mean that one would have to be on the farm for a matter of 4 or 5 hours and working fairly constantly throughout that time; but it would be time well spent. It made a difference between producing something worth while and producing evidence which was of questionable value.

The Opener

Mr. L. E. A. Rowson, in opening the discussion, said it was always an extremely difficult matter to integrate laboratory tests with practical conditions in the field, and the author had described a great many of the difficulties which must of necessity arise. Among the conditions described was the lack of protrusion of the penis of the bull, and that was certainly not uncommon. In adult bulls it did not appear to bear any relationship to the retractor penis muscles as resection of these did not appear to effect a cure. It was equally not associated with the length of the penis, but the possibility of adhesions could not be completely ruled out, because in some instances of that condition, slight bleeding from the sheath followed collection. There was another condition which had been noticed in a number of animals and which was not necessarily associated with imperfect protrusion. It was the inability of the bull to locate the vulva. The penis seemed to strike about 4 inches too low and the bull found it impossible to serve. Although, as the author mentioned, in some cases that might be associated with a pendulous abdomen, it was by no means always the case, and Mr. Rowson had seen that condition in several bulls which had been used for long periods in A.I. centres and had then been returned to natural service. In two cases it was necessary to slaughter the bulls because it was impossible to get them to serve, and in neither case was there any evidence of a pendulous abdomen.

There were two other conditions to which he desired to draw attention, and which were usually seen in older bulls. The first was noticeable when the animals were turned sharply. It could then be seen that their hind legs tended to give way, and the bull would stagger for a few steps before recovering. If the animal walked in a straight line there was nothing obvious, but when turned it was observed that the legs did not co-ordinate. Unfortunately, owing to the difficulty of obtaining *post-mortem* material in the case of such animals, he had only seen two such bulls at slaughter, and in both cases there was complete fusion of the lumbar vertabrae and their lateral processes. It was not inconceivable that these exostoses affected the foramina through which nerves passed from the spinal cord to the hind legs.

The second condition was not uncommonly seen in A.I. centres and was most prominent as the bull rose from resting. It was rather important because frequently on a farm one would not see a bull immediately it rose. The condition was such that the animal appeared to have some difficulty in pulling his hind legs under him, and he frequently extended one or the other backwards, the whole leg showing considerable trembling. Both those conditions appeared to be progressive, and in his view they constituted a very severe unsoundness.

It was always difficult to give an opinion on the fertility of a bull under about 15 months of age, and no doubt it was for that reason that the Ministry no longer carried out such tests on young bulls submitted for artificial insemination. The quality and quantity of semen could vary greatly, but it was frequently found that a rather low sperm count was obtained with good individual activity. The problem was, in his view, to a certain extent associated with the difficulty of getting such young bulls to give a clean thrust on service, and they frequently gave a half-thrust with ejaculation halfway along the artificial vagina. In most cases when that happened one obtained a false semen picture, and it was an argument for using a shorter vagina.

In the vast majority of cases semen quality rapidly improved and reached satisfactory levels by the time the bull was about 20 months old. It was of interest, perhaps, to note that in some work which Dr. Mann and he carried out on identical twin bull calves fed on differing planes of nutrition, that although the first appearance of sperm in the low plane animal was only slightly behind that of its high plane twin, quantitative sperm production was still lagging behind several months later. In an earlier experiment, Mann and Walton fed an adult bull on a restricted diet so that it lost 25 per cent. of its total weight, and in that animal the effect on the sperm was practically nil, although there was a considerable effect on the accessory glands in the production of fructose and citric acid. That experiment was not related to fertility, but it was being repeated in an attempt to relate this effect to fertility. In the case of the young bulls the link between hormones and the production

of the substance in the accessory fluid should not be overlooked.

The author had outlined many of the tests which might be used to assess fertility, but the bulk of these could not be applied in the field, and even in the laboratory must be applied within a very limited space of time. Unless conditions could be reasonably standardised, then comparison became impossible, and that, together with the fact that their relationship to fertility was not in general of a high order, rendered most of them of little value to the busy practitioner. He must, to a large extent, rely on the microscope and morphology following stained procedures.

The author had rightly pointed out the necessity of careful handling of the semen when it was obtained, particularly as regards temperature control, and that could not be emphasised too much. It was easy enough to find abnormalities in bull semen without creating one's own! It was absolutely essential to stain samples and examine under the high power, however inclined one might be to regard the bulls as fertile, because the semen showed good activity under low-power magnification.

With regard to a number of the subsequent tests referred to, they could not be applied if the semen were diluted, and to a large extent that also applied in the case of the staining techniques, in that it was difficult to obtain satisfactory staining with semen which had been diluted. There was a great deal of evidence that bulls having a relatively high percentage of abnormalities in their sperm frequently gave a low conception rate, despite the fact that the numbers of normal sperm were above the minimum necessary to give normal fertility by artificial insemination. It was not known why, if there were an excess of normal sperm, normal fertility did not follow.

Slide 1. Figures in the slide showed that to be the case. The figures were taken from the Milk Marketing Board Production Division Report, and it would be seen that where the abnormals exceeded 20 per cent., the fertility levels were below 50 per cent. in most cases. It again illustrated the necessity of morphological examination.

Two characters in particular could constitute a hazard in practice where rapid examinations of sperm were being carried out. The first was the so-called "knobbed sperm" about which much had been written. It was necessary to exercise a great amount of care because it was easy to miss the condition if one looked at the sperm casually—even under high power.

Slide 2. It was essential to stain and to examine very carefully under high power to make sure that they were visible. One could observe that the knobbed sperm of the Friesian breed for example might show normal activity, yet the bull could be sterile.

Slide 3. The second abnormality which could give rise to mistakes was a condition which occurred in Guernsey bulls. In that case the tails were quite active although separated from the head and a quick examination under low power might not reveal the condition due to the masking effect of tail movement.

It would be of interest if the author could state what he considered to be the significance of droplets in bull semen. Were they of great significance or not?

One other feature of which Mr. Rowson had had very little personal experience but which colleagues had encountered in beef bulls was a tendency to find increasing numbers of bulls showing a high proportion of decapitated sperms. It was well known that if the testes of the male were insulated, one of the first abnormalities seen in the semen was the appearance of decapitated spermatozoa and what appeared to be happening in these beef bulls was that the considerable amount of fat around the scrotum was having a similar insulating effect. All those who had anything to do with those beef breeds were aware of the wedge-shaped appearance of the scrotum of such bulls, and one could not but wonder whether the breeder by selection was not, in fact, creating his own infertility problems.

In his opinion it was not advisable to express a view on the relative fertility of a bull whose semen was within normal limits. Those who worked in artificial insemination were all aware of many bulls showing semen of excellent quality, but which had a relatively low fertility rate. Equally, it was known that many bulls, particularly in the beef breeds, produced semen which could be classified as poor yet which showed extremely high fertility. These were bulls in which no disease was known to exist.

He did not intend to go into the question of specific diseases, but when thinking of the past literature it should be borne in mind that when analysing data relating to a particular problem, one did not know whether disease existed in the herds or the centres in question, and it was necessary to look at the literature with care. While it was possible in the field to pronounce on a bull which showed a gross type of abnormality, in many cases it was difficult to distinguish the semen from a bull which would obtain a 50 per cent. conception rate and one which would obtain a 75 per cent. conception rate.

Mention had been made by the author of the part played by the transport of bulls in relation to fertility. The work of Meschaks had also indicated that transport of bulls to new surroundings might result in increased excretion of neutral steroids in the urine, and that there was often a morphological effect on the sperm themselves. There was a considerable movement of the bull between A.I. centres and from farm to centre in this country, and yet that feature appeared to be uncommon in Britain. In the United States Willett and his colleagues moved bulls from one centre to another and established their fertility rates prior and subsequent to their being moved. No difference in fertility was observed.

It was inevitable that the veterinary surgeon was from time to time faced with the problem of the bull recently purchased who was giving unsatisfactory fertility results, and where a complaint had been made by the purchaser to the auctioneer under the conditions of sale. Such cases were often very difficult in that the vendor might be able to produce evidence that the bull was satisfactory prior to the sale, and the purchaser had subsequent evidence of unsatisfactory fertility afterwards. If one ruled out the question of disease in either herds, then the position devolved to a large extent, but not completely, on the phrase "capable of getting stock," which invariably appeared in the conditions of sale. It might be useful, however, to refer to the words of a learned judge on the meaning of those words so far as the law was concerned. He said, "Clearly a bull does not fulfil that guarantee if it produces a calf only now and then. It clearly does not fail to come up to that guarantee if it does not produce a calf every time. In my view it must be a matter of degree."

Even if it could be established that the bull was perfectly satisfactory prior to sale, the matter did not necessarily end there, for under the Sale of Goods Act it might be claimed that the bull was not fit for the particular purpose for which it was sold, namely, for use as a stock bull to build up a herd. These were, however, legal matters with which veterinary surgeons need not concern themselves in any detail, except that their advice was frequently sought by clients as to whether they should press their problems into legal proceedings.

The General Discussion

Mr. G. F. Smith (Thames Ditton): "Mr. Hignett was indeed given a very difficult task in providing a paper on a subject which can be based on so many opinions. In respect of the paper I make but few comments.

"Perhaps Mr. Hignett could have mentioned in a little more detail variations in semen picture and service behaviour which seem to exist between breeds and dwelt in more detail with the 'normality' of the male reproductivity tract for the guidance of the practitioner; for a visit from the specialist can often be avoided by the most elementary examination from the veterinary surgeon on the spot.

"Mr. Hignett has referred to the effect of transport on semen production. From our experience there would seem, with very few exceptions, no great deal of evidence to substantiate this generalisation.

"Considerable detail on semen tests is given in the paper, but Mr. Hignett tends to indicate that none can be considered specific tests for predicting fertility. However, perhaps our present experience with our last 193 young bulls entering A.I. may be some guide to the efficiency of the pre-entry examination, for, of this figure, only 5 have been

disposed of during their first 6 months of A.I. life due to infertility and abnormal semen production.

"However, if we take examination in its broadest sense to take in both livestock and veterinary tests, the picture is somewhat different, for in the year ending March 31st, 1957, we subjected 255 bulls to examination and 123 were purchased for A.I. use.

"The desirability of having a set routine for examination of a bull for soundness cannot be over-emphasised. Mention could be made of identification, conformation, gait, previous history of disease and the interpretation of tests to which the bull may be subjected, *e.g.*, brucellosis and Johne's disease, and last but not least his ration in this age of hormone additives.

"No mention is made in the paper of the examination of the bull for inherited abnormalities, and in my view this should always be done with care. A careful examination of the mouth, tongue, eyes and all parts of the body is desirable.

"Finally, sir, I do with respect draw the profession's attention to the fact that many of the disputed cases are based on opinions which should *not* differ. The specialist arbitrators can well be called upon to help in cases of doubt, and it is far more advisable that cases should be settled in this way when there is, in fact, a *real* difference of opinion."

Mr. I. B. Munro (Shinfield): "Mr. Hignett and Mr. Rowson are to be congratulated on good practical papers. Although I have only had a short experience in this field, some further observations may be of use. Negrosin-eosin has been found to be of practical value in the field, not so much for obtaining an accurate estimate of the percentage of live sperm, but more for the assessment of sperm abnormalities, provided a reasonable number of live sperm were present in the samples at the time. No bull with the acrosome abnormality, referred to by Mr. Hignett, has been missed so far with this stain. By dissolving the stain in sodium citrate, as used for semen dilution, in place of distilled water, the occurrence of folded or coiled tail antifacts has been reduced, provided the stain is used within one week of preparation.

"Mr. Rowson's statement is very important, concerning the need to allow for the possible existence of infectious factors in evaluating the reports on semen tests related to fertility levels. It might be worth while repeating these tests on bulls known to be free from *Vibrio fetus* infection. In this connexion I disagree with Mr. Hignett for not recommending the test-mating of bulls for the diagnosis of this infection on economic grounds. As this is the only reliable test available its use should be advised by the profession. In some cases costs can be reduced where the owner of the bull makes a heifer available for the test, when only the sampling and culture work need be the responsibility of the veterinary surgeon."

Miss C. Ford (Sutton Bonington): "I would like first to thank Mr. Hignett for tackling this very difficult and important subject, and to congratulate him on the success with which he has tackled it. I should also like to thank Mr. Rowson for his very interesting contribution.

"Being so much less experienced than the speakers I feel more able to understand the difficulties of the non-specialist. I think Mr. Hignett underestimates the difficulty of avoiding temperature shock when you are examining semen in a draughty cart shed on some of the more primitive farms. I have given up using the "dead and alive" stain because I felt unable to standardise my technique sufficiently to avoid these pitfalls, and I would warn anyone unfamiliar with this test that it is much more difficult than you would think from hearing experts describe it.

"While appreciating that Mr. Hignett's methods result in a higher degree of accuracy, I think that a useful opinion can still be given in many cases, using a simpler and less-time-consuming technique which is more acceptable to the farmer. I examine semen on the spot for motility, but make smears and do all other tests at the laboratory usually 4 or 5 hours later.

"So long as one is not too dogmatic I think a helpful opinion can be given on about two-thirds of the bulls presented.

"When a bull's fertility is the subject of dispute I advise farmers to base their case mainly on the number of animals served unsuccessfully, and the freedom of the herd from disease.

"If I can also give an adverse report on the bull, so much the better, but if I can find nothing wrong this is unimportant, compared with his performance. In any case, my written reports, even where gross abnormalities are found, do not usually say more than, 'if this sample is typical of the bull's semen he is unlikely to be fertile.'

"Provided that both veterinary surgeons and farmers accept and understand the limitations of bull testing, I think this is a very useful procedure."

Dr. J. L. Hancock (Roslin): "I agree with Miss Ford. It is my impression that clinicians hold to the belief that measurements of semen 'quality' enable one to make certain definite statements about the fertilising capacity of a semen sample. This is not true: the best that one can do is to state one's findings in as precise a manner as possible and then to say that these findings are likely to be, or are unlikely to be, compatible with fertility.

"As regards the morphological classification of spermatozoa as 'normal' or 'abnormal' this is difficult if not impossible. It seems safer to allot spermatozoa to well-defined classes, *e.g.*, spermatozoa with bent tails or with cytoplasmic beads, knobbed spermatozoa, etc.—and to say what is the proportion of total spermatozoa in each of these classes. The findings can then be related to known standards."

The Reply

Mr. Hignett, in reply, said that in one respect he had found listening to the discussion a depressing experience, for speaker after speaker had reiterated points which he himself had made. That could have arisen from one of two causes; either some of the contributors to the discussion had not read the paper or—more likely—he had not made himself as clear as he had hoped.

There was very little in what Mr. Rowson said which called for comment. The author agreed entirely with the points made. As to the significance of protoplasmic droplets in semen, one observed free protoplasmic droplets in high fertility semen, but in his view those droplets had no significance at all.

He agreed with regard to the high incidence of decapitated sperms in some of the beef bulls.

A request was made that he should deal more fully with the specific examination of the bull. That was a very difficult thing to talk about and was easier to demonstrate if one had available a live bull. Briefly, however, he first performed a rectal examination. A rectal examination was much more simple in the bull than in the cow. He performed the rectal examination first because the bull resented that examination much less than the palpation of the scrotum. He withdrew his hand from the rectum—the bull was usually crouching and could not kick—and immediately grasped the neck of the scrotum. It was easy to palpate the testes, although he experienced difficulty in assessing the consistency of the bull's testes. In his view all bulls' testes felt softer than one imagined they should feel.

So far as penile examination was concerned, he relied chiefly on appearance. His practice was to leave all the physical examinations until after he had concluded a large part of the examination of the semen. He was at variance in that connexion with many writers on the subject, but it seemed completely wrong to upset the bull by performing those unusual manipulations, and then to expect it to work well and give a characteristic sample.

He had endeavoured to make it clear that in his view the tests and examinations which should be carried out could be done in a draughty cart shed if necessary.

He agreed that it was necessary to exercise caution in giving reports.

On the difficult question as to the importance which one should ascribe to such things as hernias, cataracts, and that type of condition, by and large with the British breeds scientific evidence that most of those conditions were hereditary was slight or absent altogether. However, his own view was that wherever possible it should be ensured that bulls with hernias and cataracts, etc., were not used for services in case those conditions were hereditary.

Myopathic Conditions in Animals

BY

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DISEASES of the musculature of farm animals appear to be more widespread than was formerly supposed. They are found as enzootics in many countries, being least common in equatorial regions. Isolated records of individual cases of myopathic disease however date back to the 1870's. Some of these diseases have now been produced experimentally and some have been prevented successfully. Despite such advances, there is no doubt that the biochemical and pathological events which lead to the degeneration of the muscle cell remain unknown. In this paper, the well-established myopathic syndromes of cattle and sheep are described. The order in which they are discussed reflects not so much their importance in causing losses in stock under field conditions, as the extent of our knowledge about their cause and prevention.

All the diseases to be described are degenerative diseases of the muscle cell which do not appear to be secondary to a neural involvement. In rare instances only is any inflammatory process to be seen. In terms of the clinical signs these diseases elicit, and in terms of the appearance and distribution of gross lesions of degeneration in cardiac and skeletal muscle, all diseases appear very similar, and exhibit similar wide ranges of severity. The use of such collective names as " white muscle disease " for them emphasises that they have usually been identified as one disease. Histologically and biochemically some distinctions can be made between them, but, even here, one cannot but fail to be impressed by the relatively small range to be seen in the pattern of degeneration of the muscle cell which takes place. The distinctions between the diseases described here are made largely on the basis of the predisposing factors concerned in their aetiology, though in some instances, there are differences in pathological findings which appear to warrant their separation.

Toxicity of Unsaturated Fatty Acids

Unsaturated fatty acid toxicity is by far the best understood of those diseases which cause muscular degeneration, largely because it can be readily produced under experimental conditions. When cod-liver oil is added to a ration containing very little vitamin E, after a variable length of time a widespread degeneration of skeletal cardiac and diaphragmatic muscle takes place. A similar effect can be produced by feeding lard as a source of fat or by feeding linseed oil (Marston & Peirce, 1942). Fractionation studies with both cod-liver oil and pig-liver fat have shown that the effect is associated with a highly unsaturated fatty acid fraction of the oil (Blaxter, Brown & MacDonald, 1953b ; Dam, 1944). Cod-liver oil contains a considerable proportion of very highly unsaturated acids in the C_{20} and C_{22} series, lard also contains these together with poly-unsaturated acids in the C_{18} series. In linseed oil, the polyunsaturated acids are largely in the C_{18} series (Hilditch, 1949). Such a disease has been produced in calves (Blaxter, Watts & Wood, 1951, 1952 ; Safford, Swingle & Marsh, 1954), in lambs (Culik, Bacigalupo, Thorp, Luecke & Nelson, 1951 ; Draper, James & Johnson, 1952) and in pigs as well, where cod-liver oil also gives rise to exudative diathesis (Garton & Naftalin, 1953). Indeed, there is now evidence to show that similar sorts of ration to those given above produce muscular degeneration in some 15 different species, ranging from tree kangaroos to the familiar guinea-pig, rabbit and hamster of the laboratory (Mason, 1951–2). There is some evidence too that the human baby is by no means immune to the toxic properties of cod-liver oil (Agduhr, 1926 ; Malmberg, 1929).

A prerequisite for the appearance of the degeneration is that the diet containing unsaturated fat should be low in vitamin E content, and the degeneration can be prevented by adding α-tocopherol or its esters to the diet. Furthermore, there appears to be a close quantitative relationship between the amount of unsaturated fat given and the prophylactic dose of tocopherol.

A degeneration of the muscles of rabbits, rats and hamsters can be produced by feeding them diets devoid of both fat and vitamin E providing the experiments are continued for a long time (MacKenzie, MacKenzie & McCollum, 1940, 1941). In calves, however, our experiments (Blaxter & McGill, 1955) and those of Adams, Gullickson, Sautter and Gander (1954) were not successful in producing muscular degeneration when diets free of fat and very low in vitamin E content were used. Perhaps the experiments were not carried out for sufficiently long, ours terminating at four months. It may be pointed out, however, that vitamin E deficiency in cattle produced in the absence of a dietary source of fat does eventually lead to death from cardiac failure (Gullickson & Calverly, 1946), but widespread skeletal muscular degeneration comparable to that produced by feeding unsaturated fat was not found.

The effects of unsaturated fatty acids in producing muscular degeneration might be ascribed to an induced deficiency of vitamin E even though the effects of uncomplicated experimental vitamin E deficiency in cattle appear to be less extensive than in rabbit experiments, but this is certainly not a sufficient explanation. The usual criteria by which vitamin deficiency states are judged are firstly, tissue depletion of the vitamin and secondly, specificity of the vitamin in prophylaxis or in cure. Neither criteria suggest that unsaturated fatty acid damage is a deficiency disease in the classical sense. The toxicity of cod-liver oil in cattle can be reversed by the simultaneous administration of methylene blue (Blaxter, Brown, Wood & MacDonald, 1953), and the toxicity of lard in lambs can be reversed by diphenyl-p-phenylene-diamine (Johnson, 1955).

These two substances do not have any vitamin E activity when assayed by the classical method of assessing potency in terms of rat fertility (Harris & Mason, 1955). Furthermore, oxidation products of α-tocopherol, such as the quinone and hydroquinone are effective in preventing muscular disease in rabbits (MacKenzie, 1953 ; Milhorat, 1953) and calves (Blaxter, 1955) but are ineffective in the rat fertility assay (MacKenzie, 1953 ; Harris & Mason, 1955).

Table I summarises some of our analyses of the tocopherol content of muscles of calves with muscular degeneration induced by cod-liver oil. The tocopherol content of the muscle is certainly not diminished even in muscles undergoing degeneration, nor is the tocopherol content of the liver depleted when the muscles degenerate as a result of cod-liver oil administration. In this regard, cod-liver oil contains appreciable amounts of tocopherol (Brown, 1953a), which may account for the slightly higher concentrations in the muscle and liver fat of animals given it.

TABLE I

TOCOPHEROL CONTENT OF MUSCLE FAT AND LIVER FAT IN CALVES RECEIVING COD-LIVER OIL

	Muscle tocopherol (mg./kg. lipid)	Liver tocopherol (mg./kg. lipid)
Normal muscle (no cod-liver oil)	690	234
Degenerate muscle (cod-liver oil given)		
Slightly affected	633	255
Severely affected	860	—
Very severely affected	850	282

The conclusion appears inescapable that the muscular degeneration induced by cod-liver oil is a toxic syndrome in which vitamin E, in common with other compounds, exerts a protective action. This necessarily focuses attention on the way in which unsaturated fatty acids induce degeneration. Formation of abnormal phospholipids at cell interfaces thus interfering with the energy exchanges of the cell seems a possible explanation. Tocopherols presumably act by preventing the action of such substances or by facilitating the dissimilation or deposition of the unsaturated acids themselves.

As far as veterinary practice is concerned, cod-liver oil poisoning is not uncommon but the advent of vitamins A and D concentrates has reduced its incidence. It occurs mostly in pail-fed fattening beef calves which are given little but milk, liberally supplemented with fresh cod-liver oil. It is most common in late winter when green food is scarce and milk consequently contains little vitamin E. Replacement of the cod-liver oil with a supplement of vitamins A and D and treatment with α-tocopheryl acetate is usually effective, but where muscle degeneration has become severe the response may be very poor.

The clinical signs are those which characterise most myopathic conditions, namely severe muscular weakness and stiffness, usually with a tendency of the muscles to hypertrophy. A wide range of clinical syndromes occurs dependent upon which muscle or muscle groups are affected. The suspensory muscles of the limb girdles are those most commonly involved, and cardiac abnormalities, and heart failure are frequent. The *post-mortem* appearance of the muscle is one ranging from defined or diffuse areas of pallor to a complete creamy white appearance of the whole of one or more muscles. These lesions are always bilaterally symmetrical. Histologically, the principal change is a hyaline degeneration of the cell followed by coagulation necrosis and multiplication of the sarcolemmal nuclei. Occasionally, granular degeneration may occur (MacDonald, Blaxter, Watts, & Wood, 1952). Calcification of the lesion in cattle is very rare, and the type of degeneration described by Hjärre and Lilleengen (1936) in field cases of muscular degeneration in which there is a deposition of minute calcium granules between the myofibrils has never been seen in experimental cod-liver oil poisoning. In lambs, some calcification occurs when they are given rations containing lard (Bacigalupo & Luecke, 1954) and in rabbits calcification is usually marked (Fenn & Goettsch, 1937). Regenerative and degenerative changes can be seen in the same section and the most striking feature of the lesion is the way in which individual fibres degenerate while others appear quite normal.

Enzootic Muscular Dystrophy in North East Scotland

The second muscular disease to be discussed is one which occurs in the beef herds in N.E. Scotland. Here the method of husbandry is to suckle the calves on their dams from when they are born in January to April until they are weaned off grass in the late summer (Sharman, 1954). During the winter, which tends to be long, the cows are stall fed on traditional rations of turnips and straw. A large number of such farms have difficulties in raising their calves because they develop a muscular disease which has been called enzootic muscular dystrophy. The disease does not occur in out-wintered stock and is very rare in stock given rations of good quality silage. The prerequisites are in-wintering of stock, and the feeding of the cows on turnips and straw. The disease in the calves is not hereditary in origin. Clinically, and pathologically, the muscle degeneration is comparable to that produced by cod-liver oil poisoning, being hyaline, with a marked sarcolemmal reaction and with no calcification of the lesion.

As with the cod-liver oil disease, prophylactic therapy with α-tocopherol acetate was found to be successful (Blaxter & Sharman, 1953). Three years' experimental work, involving about 500 cattle, was carried out and it was found that dosage of the cow with α-tocopherol during the last six weeks of pregnancy prevented the disease, and dosage of the calf with either 150 mg. or 20 mg. α-tocopherol acetate also prevented it. Dosage with 10mg. α-tocopherol acetate was not completely effective in preventing the disease, though it reduced its incidence from 19·6 to 6·1 per cent and prevented deaths.

Attention was first paid to the tocopherol status of the cow and her calf, and to the dietary intake of vitamin E by the cow and calf. Comparisons were made between in-wintered herds feeding turnips and straw, where the disease occurred and other herds in the same district feeding silage where the disease was absent. Further

comparison was made with herds in West Scotland where the disease is unknown. Some of the results of these investigations (Blaxter, Cowlishaw, Hutcheson & Sharman, 1955) are summarised in Tables II and III and in Figure 1. They show that on the farms feeding their cows on turnips and straw, the tocopherol content of the blood of the cow prepartum, the colostrum and the blood of the calf at birth were about one-tenth that found in herds not experiencing the disease, and that prevention of the disease by giving the cow tocopherol also restored blood and colostral tocopherols to more normal levels. The content of tocopherol in the whole milk was very low indeed, and only recovered when the cows went to grass in the spring. Furthermore, the liver tocopherol of calves which died at birth was extremely low, and, when calves from these farms were given tocopherol the resultant increase in serum tocopherol was very small, suggesting that they were depleted of the vitamin.

TABLE II

THE TOCOPHEROL STATUS OF HERDS IN N.E. SCOTLAND AND IN W. SCOTLAND

	Serum of cow within 24 hours of parturition; concentration of tocopherols (μg./100 ml.)	Colostral tocopherols (μg./100 ml.)
Turnip and straw farms, N.E. Scotland	75	27
Same + α-tocopherol acetate	252	316
Silage farms, N.E. Scotland	215	
W. Scotland farms, winter rations	324	408
W. Scotland farms, grass	653	645

TABLE III

CONCENTRATION OF TOCOPHEROL IN THE MILK FAT OF COWS ON FARMS FEEDING TURNIPS AND STRAW

Time of sampling	Number of samples	Mean tocopherol content of milk fat (μg./g.)
23rd March—3rd April	9	5·6
7th April—20th April	9	3·5
21st April—4th May	18	5·0
5th May—18th May	7	7·1
19th May— 1st June	3*	14·5
2nd June—25th June	3*	24·6
W. Scotland farms, winter	20	25–30
W. Scotland farms, summer	20	30–45

* Cows at grass

These results might suggest that the disease could be regarded as a primary deficiency of tocopherol, but this explanation is an over-simplification for several reasons. Firstly, there is the evidence already cited that muscle disease could not be produced experimentally within a four-month period by giving fat-free rations containing very little vitamin E. Secondly, the experiments in which 10 mg. α-tocopherol were given did not protect a number of calves, and yet calves on the same farms which received no supplementary vitamin survived. Thirdly, it was not possible to differentiate between potentially dystrophic calves and normal ones even on the same farm on the basis of their blood serum tocopherol concentrations. Table IV summarises mean values and ranges of serum tocopherol in untreated calves on the same farms, classified according to whether they developed dystrophy or not. There was certainly no clear-cut differentiation. Calves with less than 5 μg. per 100 per ml. blood might survive, and calves with 50 μg. per 100 per ml. might succumb. The only generalisation possible from the results of many thousands of analyses was that if the concentration of tocopherol exceeded 70 μg. per 100 per ml. then the possibility of muscular dystrophy occurring could be regarded as very small. An investigation of the tocopherol content of the milk of range cattle in Montana showed a similar general parallelism between tocopherol levels and dystrophy incidence (Swingle, Safford & McRoberts, 1956).

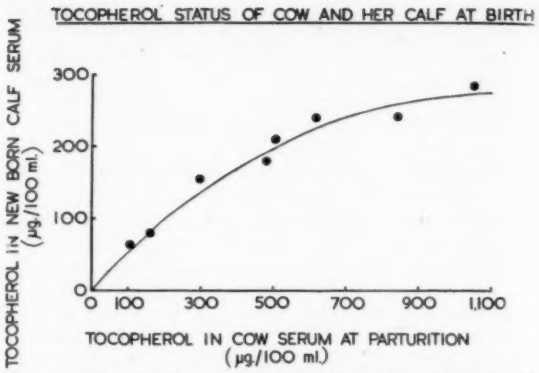
TOCOPHEROL STATUS OF COW AND HER CALF AT BIRTH
TOCOPHEROL IN NEW BORN CALF SERUM (μg./100 ml.)
300
200
100
0
0 100 300 500 700 900 1,100
TOCOPHEROL IN COW SERUM AT PARTURITION (μg./100 ml.)

FIG. 1.—Relation between tocopherol content of serum of cow at parturition and that in the calf at birth. Each point represents the means of at least five cows from one or more herds.

TABLE IV

THE TOCOPHEROL CONTENT OF THE BLOOD SERUM OF CALVES WHICH SUBSEQUENTLY DEVELOPED MUSCULAR DYSTROPHY AND OF CALVES ON THE SAME FARM WHICH DID NOT

	Calves which developed muscular dystrophy	Calves on the same farms which did not develop dystrophy
Number of calves	15	15
Mean tocopherol content of serum (μg./100 ml.)	25·1	31·1
Range	<5–61	<5–72

In view of the association of a comparable muscular degeneration with unsaturation of the dietary fat, the milk fats and blood fats were next examined. It was found that the milk fats of cows given turnips and straw were, in fact, less unsaturated than the fats of those given silage. Nor was any evidence that the blood serum fats of calves from dams given turnips and straw contained more polyethenoid acids than those

from dams given silage. There was some evidence, however, that tocopherol administration reduced the concentration of polyethenoid acids in the blood serum lipids (Garton, Duncan, Blaxter, McGill, Sharman & Hutcheson, 1956). What was most striking was again the large difference in the tocopherol content of the milk fats of the cows given the two types of ration. Milk fat produced on turnips and straw rations does nevertheless contain polyunsaturated acids in both the C_{18} and C_{20}–C_{22} series in small amounts (2 to 3 per cent.) and it may be that these are concerned in the production of enzootic muscular dystrophy. In this regard, milk which has been oxygenated, and which as a result can contain little tocopherol, when fed to calves produces the muscle degeneration (Hjärre & Lilleengen, 1936). This might suggest that the unsaturated acids normally present in milk fat are responsible, but only exert their effect when the fats are very low in vitamin E content.

One further factor in the aetiology of the disease deserves mention, since it is common to certain other muscular diseases. This is muscular exertion. The disease is invariably one of in-wintered animals, which are closely confined in warm surroundings. Maximal incidence of the disease occurs when the calves are turned out to pasture for the first time, when several cases often occur in a matter of hours. The unaccustomed muscular exertion and the effect of cold on muscle metabolism are clearly factors to be considered. What is, however, certain is that prophylactic therapy with vitamin E prevents the disease.

Stiff Lamb Disease

The third disease of the muscles to be discussed is one which occurs in the Northern States of the United States and in Scandinavian countries, again under a particular pattern of husbandry conditions. This consists of the pen or indoor feeding of pregnant ewes with rations of different hays and concentrates and their subsequent pasture feeding in summer. The disease becomes manifest in the lambs during the first two months of life. It is predominantly a disease of in-wintering which is the probable reason for its virtual absence in Britain (Cotchin, 1948). It was shown by Cornell workers that the disease could be prevented by giving vitamin E to the pregnant ewe and cured by giving vitamin E to the lamb (Willman, Loosli, Asdell, Morrison & Olafson, 1945, 1946). This was amply confirmed by Swedish investigators (Swahn, Obel & Wanntorp, 1948).

When the rations of the pregnant ewes were examined to find whether or not the disease could be regarded as a dietary deficiency of vitamin E some surprising results were obtained. Swahn *et al.* could detect no differences in tocopherol content between hays fed to ewes on farms where the disease was present and those given on farms free of the disease. Nor could the American workers find differences in the tocopherol content of the rations which produced the disease and those which did not. Later analyses by Brown (1953b) suggested, in fact, that the normal rations given in the American work probably contained less α-tocopherol, the most potent of the seven naturally occurring tocopherols (Green, 1955) than did the "stiff lamb ration." Studies in Montana (Safford, Swingle & McRoberts, 1956) have further shown a complete absence of correlation between the tocopherol content of the milk of the ewe and the incidence of the disease in the lamb.

Despite these anomalies, there is ample evidence that the disease is of dietary origin associated with some ration ingredients and never found when others are given. Ingredients which are free from suspicion are timothy hay, maize, maize silage, wheat germ and wheat bran together with certain native hays. Wheat germ and wheat bran prevent the disease when given with incriminated ingredients. Incriminated ingredients are legume hays, both clover and alfalfa, beans and barley. Oats appear to protect when added to alfalfa hays but not to clover hays (Safford *et al.*, 1956 ; Willman *et al.*, 1945).

A further aspect of the disease is that as in the instance of enzootic muscular dystrophy cattle in N.E. Scotland, exercise precipitates the overt signs of the disease (Warner, 1953). Furthermore as in the enzootic disease of cattle, maximal incidence occurs during the first 48 hours after release of the animals from their winter quarters.

No studies have yet been made of the dietary factors other than tocopherol which may be involved in the disease. It does appear, however, that the disease is of dietary origin, that it is prevented by α-tocopherol and exacerbated by unaccustomed exercise. Histologically the disease is characterised by hyaline degeneration of the muscle cell.

Stiff Lamb Disease on Pasture

In New Zealand, Hartley (1953) has described a muscular degeneration occurring in lambs carried on legume pasture. A similar disease has been noted in lambs on irrigated pasture in Oregon (Muth, 1955). To quote Hartley, "it would be difficult to postulate an uncomplicated vitamin E deficiency under these conditions." There is, however, an association with muscular exertion since the disease is usually apparent in New Zealand after the animals have been driven for long distances. No detailed studies of aetiological factors have been made.

White Muscle Disease in Oregon Cattle

Muth (1955) has described "white muscle disease" in Oregon cattle which, while clinically comparable to that noted in cattle in N.E. Scotland, deviates from it in many respects, and appears more comparable to descriptions of a naturally occurring disease described in cattle by Hjärre and Lilleengen in 1936 and by early German workers. In the first place, the sequence of hyaline or Zenker's degeneration followed by sarcolemmal proliferation which occurs in the diseases mentioned so far is not found, but instead there is what appears to be a primary calcification of the muscle fibre. Muth reports, "Rows of granules are seen in some instances completely filling the sarcolemma without disturbing the architecture." Complete loss of sarcoplasm can occur leaving only a sparse matrix of connective tissue and a dense capillary network with a scattering of inflammatory cells. There is no massive reaction on the part of the sarcolemmal nuclei

as in cod-liver oil poisoning or in the Scottish disease. The Oregon disease occurs on irrigated farms in a restricted area, the pasture containing a very high proportion of legumes and being intensively fertilised. Its cause is at present unknown but it does not appear to respond to vitamin E therapy (Muth, 1957). Presumptive evidence would suggest very high levels of vitamin E in these pastures and in the crops obtained from them. The lesions are often present at birth.

Muscular Dystrophy of Hoggs

A degeneration of the muscles of hoggs occurring under a particular set of husbandry conditions was observed in Scotland. The hoggs were wintered on turnips or turnips and hay and were then subjected to exercise or were transported long distances (Graham Marr, Sharman & Blaxter, 1956). The lesion differed from that in cattle wintered on rations low in vitamin E content, in that although showing widespread hyaline degeneration, the sarcolemmal reaction was poor and there was widespread calcification. In some fibres calcium deposition had taken place within them to the extent that the whole fibre was calcified. A disease described by Dodd (1954) in New Zealand appears comparable, in that the hoggs were wintered on turnips and swedes and then transported by rail. The fact that a low tocopherol diet was given, and the animals were then subjected to muscular stress suggests similarities with the enzootic cattle disease of N.E. Scotland.

Generalised Myopathy of Adult Sheep

Bosanquet, Daniel and Parry (1956a, b.) and Parry (1957) have described a myopathy in adult sheep which appears to be of widespread occurrence. It has been identified in part as a component of the scrapie syndrome, but this provisional identification is of no concern in the present context. Grossly and histopathologically the lesion appears comparable to that seen in cod-liver oil poisoning and enzootic muscular dystrophy in that it is non-inflammatory, there is hyaline swelling, sometimes granular degeneration, a marked reaction of the sarcolemma and never any calcification. The postural and gait defects are comparable to those seen in other myopathies and the disease has been classified, largely on clinical grounds, into six or nine main types (Parry, 1957). Cardiac abnormalities, however, appear to be rare, being limited to foci of diffuse pallor of the myocardium.

The aetiology of this disease, if it is indeed one entity, is completely unknown. There is some suggestion that it is of hereditary origin but this has not yet been fully substantiated. There is no evidence to suggest a particular ration ingredient is involved, if it is of nutritional origin. Curative tests with vitamin E have not been successful, but no prophylactic experiments have been made.

Discussion

The seven myopathic conditions of cattle and sheep described above by no means limit the types of muscular degeneration which may occur. We have, for instance, encountered isolated cases of degenerative muscle disease in cattle in which the muscle is completely atrophied to be replaced by fat and fibrous tissue, resulting in severe contractures. Similarly, French and German workers have described other types of degeneration characterised by marked inflammatory reactions. Nor does the implication of vitamin E, polyunsaturated fatty acids and unaccustomed strain on the muscles limit the number of aetiological factors. It appears, for instance, that pasture legumes and legume hays have a positive effect in producing the disease under some conditions. Furthermore, we have been able to produce mild muscular degeneration in calves by means as diverse as experimental anoxia and experimental potassium deficiency.

The histological findings in the seven diseases show that the pattern of degeneration in any one disease has a remarkable variation, but that similar changes can be seen to a varying degree in almost all the diseases studied. An exception is the Oregon muscular dystrophy in which the primary change seems to be calcification of the sarcolemma. Even so, this change can be seen in sheep with stiff lamb disease or in the disease of hoggs. This relatively limited range of lesion has been commented on by pathologists before. Thus Walton and Adams (1956) state, "Muscle can have but a limited repertoire of response to a variety of noxious agent." These workers have also pointed out that differences in the histological appearance of muscle fibres in human myopathies appear to reflect variation in the severity and rapidity of onset of a series of processes which can be attributed to a similar basic histological lesion. The results presented above are in general agreement with this hypothesis.

A limited range in the histological findings in the different diseases, together with close similarity in the clinical syndrome the lesions cause, necessarily means that considerable emphasis must be placed on their aetiology in order to classify them in an adequate way. In this regard, unlike human muscular dystrophies (Stevenson, 1953; Walton, 1955, 1956), the myopathies of farm live-stock do not appear to be hereditary diseases but rather of complex nutritional and managerial origin. A possible exception is the myopathy of adult sheep under investigation by Dr. Parry. The diseases are all far more acute than human muscular dystrophies which may take several years or decades to develop and affected animals can and do recover from them. They thus appear more comparable to several of the non-inflammatory types of myositis in man rather than the muscular dystrophies (Adams, Denny-Brown & Pearson, 1953). The localisation of the diseases in particular geographical areas appears referable to common husbandry methods rather than to a familial tendency in the stock concerned.

From the evidence presented there appear to be four factors concerned in the aetiology of these diseases, and none of these are common to all. A relative lack of vitamin E is certainly concerned in three of the diseases, unsaturated fatty acid toxicity, enzootic muscular dystrophy, and classical stiff lamb disease. It is possibly involved in the hogg disease too. It does not appear to be of great importance in the Oregon disease or in stiff lamb disease under New Zealand conditions. Unaccustomed muscular exertion appears to be involved in four of the diseases, the exceptions being unsaturated fatty acid toxicity, the Oregon disease and the generalised myopathy of sheep. The

third factor, the presence of legumes in the diet appears to be concerned in both types of stiff lamb disease and in the Oregon disease of cattle. Finally the presence of polyunsaturated fatty acids in the diet is unequivocally bound up with the appearance of myopathy in animals given cod-liver oil and other unsaturated fats, and it may be that the unsaturation of milk fats may make the young animal given milk susceptible to a lack of vitamin E in the diet. Furthermore, it is well known that the leaf fats of pasture herbage are highly unsaturated (Hilditch, 1949) which suggests that unsaturated fatty acids may be concerned in the diseases occurring at pasture. No doubt further researches will elucidate the exact pattern of cause, and make our knowledge of these myopathies less fragmentary than it is to-day.

Summary

Seven syndromes in cattle and sheep are described. These are, unsaturated fatty acid toxicity, usually met under field conditions when cod-liver oil is given, the enzootic muscular dystrophy of beef cattle of N.E. Scotland, the stiff lamb disease occurring after in-wintering of ewes, a comparable disease occurring at pasture in New Zealand, the white muscle disease of Oregon, muscular degeneration in hoggs in Scotland, and the generalised myopathy of adult sheep described by Bosanquet, Daniel and Parry (1956).

It is pointed out that these diseases cannot usually be distinguished on clinical pathological or histopathological grounds alone, because muscle appears to have but a limited range of response to many different factors. This necessarily places considerable emphasis on their aetiology in any attempt to classify them. Four aetiological factors appear to be concerned severally or together in these diseases, a very low tocopherol intake, a high intake of polyunsaturated fatty acids, unaccustomed muscular exertion after close confinement, and a ration during pregnancy of certain legumes. These four factors do not, however, exhaust the number of known aetiological agents in the production of myopathy. Unlike human muscular dystrophies, there is little evidence to suggest they are of hereditary origin. Where sufficient information is available the diseases all appear to be of complex nutritional and managerial origin.

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THE SPEAKER'S INTRODUCTION

Dr. Blaxter, presenting the paper, explained that in talking about the various types of muscular disease which occurred in farm animals he thought he could do no better than show some ciné pictures, and a series of slides illustrative of the enzootic dystrophy in beef cattle in the North of Scotland. Another series of slides would show the essential similarity of the lesion of the muscle in a variety of species. If time then permitted, he would then make some final remarks on the aetiology.

The film and the slides having been displayed, with explanatory remarks by the author, Dr. Blaxter went on to say that in the paper he had listed 7 diseases which, clinically, showed a very considerable similarity since an animal could react only in a limited number of ways to a lesion of the muscle. With one exception, the diseases were similar histologically. In this regard several pathologists had pointed out that muscle had only a very limited repertoire of response to quite a variety of noxious agents. In cattle, it had, in fact, proved possible to produce muscular degeneration of a comparable type by diverse means, including capillary blockade, experimental anoxia and experimental potassium deficiency.

Clinical appearance and the histological examination of the muscle did not provide adequate criteria on which differential diagnosis could be based. Very great weight must therefore be placed on the particular aetiological factors which were concerned. From their own work and that done overseas, these aetiological factors could be limited to 4. The first quite clearly involved vitamin E, and the disease in the North of Scotland could be prevented by giving either 20 mg. or 150 mg. of alpha tocopherol orally every 24 hours. Similarly, the American work showed without any doubt that vitamin E preparations would both prevent and cure stiff lamb disease. That would suggest that these might be deficiency diseases but one could not assume that that was so for several reasons.

It was quite true that in Inverness-shire the vitamin E content of the ration was extremely low. During the winter, the cows received a diet of turnips and straw which contained only about one-tenth of the vitamin E in the rations which cows in Central and West Scotland received. As a result, the transfer of vitamin E in the colostrum to the calf was extremely low, and the content in the calf's blood —probably one of the best measures of the status of the animal—was only about one-fifth of that in more adequately fed herds.

There seemed to be evidence that precipitating factors were involved in that although some animals had low blood tocopherol content they did not necessarily develop the disease. The precipitating factor did not appear to be an excess of unsaturated fatty acids, in this instance. One factor was certainly muscular exertion. Anything which induced a strain on the muscle, particularly cold, and the exercise which the animal had when it first went out to pasture led to an exacerbation of clinical signs. A further factor appeared to be the presence of certain legumes in the diet. This had been noted both in New Zealand and in America, and there was some evidence in the North of Scotland that legumes might be associated with some outbreaks of the disease occurring there.

The Opener

Dr. John N. Walton, of the Royal Victoria Infirmary, Newcastle upon Tyne, said: "May I begin by thanking the B.V.A. for their kindness in inviting me to address you to-day on the subject of muscle disease in man. It is of the greatest importance to those of us who are interested in the human myopathies that we should be able to determine the relationships which exist between these conditions in man and the similar disorders which occur in animals. Not only may your studies of the myopathies seen in veterinary practice throw important light upon the aetiology and pathogenesis of human diseases which are at present incurable, but you may also be able to provide us with animals which can be utilised in future trials of new remedies.

Muscular Dystrophy

"I will begin by discussing muscular dystrophy, which is probably the most important and best recognised muscular disease in man. I must say at once that human muscular dystrophy is very different from the large group of conditions to which this title is applied in animals. It is different in that it is a progressive, incurable disorder which is genetically determined and there is now ample evidence to show that deficiency of vitamin E plays no part in its causation. Its progressive course, which results in increasing muscular weakness and often eventual total disablement, makes it one of the most distressing and frustrating diseases known to medical science, particularly since, although we know that it is inherited, we have remarkably little evidence as to the means by which the gene responsible for the disease produces its effects upon the muscles.

"Although we know so little about aetiology, recent work has defined more clearly the various forms of the disease, which vary widely in clinical course and in mode of inheritance (Walton & Nattrass, 1954). It is broadly true, nevertheless, that all forms of the disease produce similar pathological changes in the affected muscles; furthermore, they all affect principally the shoulder and pelvic girdles and the proximal muscles of the limbs, so that affected individuals develop a characteristic waddling gait, fall easily, have difficulty in climbing stairs and in rising from the floor, and find it difficult to raise the arms above the head.

"The first and most severe form of muscular dystrophy is the pseudohypertrophic or Duchenne type which affects boys in the first few years of life, and is transmitted as a sex-linked recessive character, being carried by females, but manifest in males. Characteristically, there may be enlargement of certain muscles, particularly the calves, but others are atrophic and weak; however, the term 'pseudohypertrophic' is an unsatisfactory title for this form of the disease, as some pseudohypertrophy or muscular enlargement may occur in any form of dystrophy. The disease progresses relatively quickly so that the affected individuals generally lose the ability to walk and become seriously disabled during the second decade. Death follows, sooner or later, from respiratory infection.

"The second is the limb-girdle type which usually begins in adolescence or adult life, affects the sexes equally, is inherited as an autosomal recessive character, and may begin in either the upper or lower limbs. It is less rapidly progressive than the Duchenne type but generally produces severe disability in middle life.

"The third and mildest form is the facioscapulohumeral, which affects the face as well as the shoulder girdle and later spreads to the pelvic girdle; it may begin at any age and in either sex, and is transmitted as an autosomal dominant character, from one generation to the next. Abortive cases occur in which only a few muscles are affected and the disease fails to progress; indeed such individuals may be quite unaware that they are suffering from the condition. Most patients, however, become progressively weaker, though they may survive and remain active to a normal age.

"I must also mention at this point dystrophia myotonia, a condition of adult life and of dominant inheritance, in which a muscular dystrophy of the peripheral part of the limbs is combined with frontal baldness in the male, cataracts, atrophy of the gonads and the phenomenon of myotonia, which produces a delay in muscular relaxation. I shall mention myotonia again later.

"In all of these forms of muscular dystrophy degeneration of muscle fibres occurs, but is relatively inconspicuous when compared with that seen in the animal diseases, and the muscular changes are more often characterised by a striking variation in diameter of muscle fibres, with fatty infiltration and very little cellular reaction of any description. The segmental areas of degeneration of muscle fibres which do occur in the more rapidly progressive cases, however, are very like those of the experimental vitamin E deficiency myopathy; this similarity does not, of course, imply a common aetiology, but merely underlines the fact that muscle is a tissue which has a limited repertoire of response to a variety of pathogenic agents. Biochemically, too, there is little which is specific; creatinuria occurs, the muscle cell loses potassium, the serum aldolase is increased and the intramuscular aldolase is diminished, while some cases excrete ribose in the urine. The significance of these findings remains in doubt.

"Certainly there is ample evidence that human muscular dystrophy is an entirely different disease from most of those muscular degenerations which occur naturally in animals (Blaxter & McGill, 1955) and no naturally-occurring vitamin E deficiency myopathy has been reported in man. The fact that scrapie may possibly be an inherited disorder (Bosanquet, Daniel & Parry, 1956) suggests a resemblance to the human disease but the pathological changes seen in the

muscles of affected sheep are much more striking and acute than those seen in human dystrophy. The inherited myopathy of mice recently reported from Bar Harbor, Maine, by Michelson, Russell and Harman (1955) shows much closer affinities to the human disease.

Polymyositis

It will now be appropriate to mention polymyositis, a disease which may resemble muscular dystrophy very closely, but which is entirely different in aetiology, may recover spontaneously, or may respond to treatment with cortisone or ACTH. This disease, which has come into prominence in recent years (Adams, Denny-Brown & Pearson, 1953), probably accounts for most of the reported examples of reovery from 'muscular dystrophy' (Nattrass, 1954). In other words, these cases have often been wrongly diagnosed in the past. This condition, like muscular dystrophy, affects the girdle and proximal limb muscles; it can occur in either sex and at any age, but is commoner in females. It tends to progress more rapidly than muscular dystrophy, and may give rise to muscular pain and tenderness, difficulty in swallowing, joint pains and a skin rash, but any or all of the latter features may be absent and the resemblance to dystrophy may be so close that diagnosis must depend upon ancillary investigations. Of these, electromyography, a technique of recording the electrical activity of muscle by means of a needle electrode inserted into it, and muscle biopsy, are the most important. The pathological changes revealed by muscle biopsy are generally different from those of muscular dystrophy; the degenerative lesion of the muscle fibre is similar but these changes are, as a rule, more severe and extensive in polymyositis; in addition thefe is infiltration with inflammatory cells, between the muscle fibres and around blood vessels, as well as active muscle regeneration. Furthermore, the erythrocyte sedimentation rate is often raised in such cases, as is the serum γ-globulin.

"There is ample evidence available to indicate that human polymyositis is not usually due to specific infection with a bacterium or virus, nor is it a deficiency disease. Indeed it is apparent that this disease is related to others in the 'collagen' or 'connective tissue' group, which includes diseases such as rheumatoid arthritis, scleroderma and disseminated lupus erythematosus (Walton, 1956). It seems that this group of diseases is in a sense due to an allergic inflammation, resulting from a hypersensitivity response to a wide variety of allergens. It is of some interest that malignant disease seems to act as a sensitising agent in some cases; polymyositis and malignant neoplasms, particularly in the lungs, are associated more often than could be accounted for by chance. Despite the striking similarity of the pathological changes seen in this disease in man to those observed in certain animal forms of muscular dystrophy and polymyositis, the latter seem in general to be deficiency diseases and I am not aware that allergic or hypersensitivity diseases of this type have been described in animals.

Paroxysmal Idiopathic Myoglobinuria

"I mention this disorder simply in order to confirm that a condition occurs in man which seems closely comparable to the paralytic myoglobinuria which occurs in horses (Carlström, 1930). Patients with this condition suffer repeated episodes of muscular pain and weakness and pass large quantities of myoglobin in the urine; pathologically, focal degeneration of muscle fibres can be demonstrated. The aetiology of the condition remains obscure.

Myotonia

"I have mentioned already that in dystrophia myotonia, a form of muscular dystrophy is combined with myotonia, a phenomenon of delayed muscular relaxation, seen best as an inability to relax the grip. In the closely related condition of myotonia congenita (Thomsen's disease), myotonia may effect all the skeletal muscles from birth. These patients are remarkably stiff and clumsy in their movements and are much worse in the cold weather. The exact cause of the phenomenon of myotonia is unknown but it seems that there may be an abnormality in the motor end-plate or in the the membrane of the muscle fibre. An exactly comparable inherited disorder has been described in certain families of goats (Brown & Harvey, 1939) and like the human condition can be relieved by quinine.

Myasthenia Gravis

"A condition which is in many ways the converse of myotonia is myasthenia gravis, in which the muscles fatigue abnormally easily. Characteristically, this disorder gives rise to weakness which is greatly increased by exertion or becomes more severe as the day wears on. Often it produces double vision, drooping of the eyelids and difficulty in swallowing. It appears to be due to a defect in conduction at the motor end-plate and can usually be corrected by treatment with prostigmine. I am not aware of the occurrence of a similar disorder in animals.

Familial Periodic Paralysis

"Another uncommon muscular condition which has not, to my knowledge, been discovered in animals, is familial periodic paralysis, in which patients experience sudden episodes of paralysis, often very extensive, of the voluntary muscles. The condition is inherited; during attacks the serum potassium is usually low and the weakness can be relieved by the administration of potassium.

Endocrine and Metabolic Myopathies

"Muscular weakness and wasting like that of muscular dystrophy can also occur in certain disorders of the endocrine glands, such as thyrotoxicosis and Addison's disease, but again, to my knowledge, disorders of this nature have not been noted in animals.

Conclusions

"We may conclude that although there are certain striking resemblances between the common muscular diseases of man and those of animals, there are, in most cases, important aetiological differences. Thus it is apparent that the commonest form of muscular dystrophy in animals is due to a deficiency of vitamin E, while human muscular dystrophy is a progressive degenerative disorder which we know to be genetically determined though its pathogenesis remains obscure. Nevertheless, there is ample reason for supposing that research in both the human and animal fields may prove to be mutually interdependent, each new discovery in one field casting new light upon outstanding problems in the other. It is for this reason that contacts of this nature are so valuable, and I would like to thank you again for the opportunity of addressing you to-day."

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The General Discussion

Mr. Oliver G. Jones (London) said: "I should like to congratulate the author of this fascinating paper for the highly efficient way in which he has laid his facts before us. I should like to bring to the notice of this meeting a condition in young lions with which I have been familiar for the last 6 years. For want of a better description it is loosely referred to as muscular dystrophy in lions. The condition usually affects young animals of either sex at the period of adolescence, namely 18 months to 2 years. It thus seems dissimilar to those recognised conditions seen in lion cubs and associated with vitamin D or mineral maladjustment.

"The affected animal will, at first, seem almost normal but just a little weak on the hind legs. Slowly, over a course of weeks, the condition progresses until in the worst type of case the animal is prostrate. There is a progressive inability properly to co-ordinate muscular action and balance, and the resulting muscular imbalance creates an appearance of loss of bodyweight, although this is by no means the case.

"There is an exaggerated posture at the shoulder regions and I was interested to hear Dr. Blaxter's comments on the position of the scapular in the cases of muscular dystrophy in groups which he has discussed. Dr. Blaxter can see a photograph of a lioness affected with muscular dystrophy at present exhibited by the Zoological Society in the Scientific Exhibition.

"There seems to be great disturbance in balance, posture and muscular control. Lions affected with muscular dystrophy are still able to eat and preserve all their natural functions unimpaired. Response to touch, light, sound and scent are all normal. I was interested in Dr. Blaxter's observations of secondary lung infection in some cases in calves; so far I have experienced only one such secondary infection.

"My colleague, Mr. Fiennes, and I, are intensely interested in this condition and are carrying out an exhaustive investigation into it. Quite recently an affected male lion had become seriously ill and was destroyed. Mr. Fiennes is carrying out a detailed *post-mortem* on this carcase, and various parts of the brain and spinal cord are being carefully sectioned. There seems to be some indication that the condition as seen in lions may be a mixture of several features some of which may be mentioned:—

1. Avitaminosis: B and/or E administration of vitamins (in particular the B group) has been tried with some success. This may be purely coincidental because as a routine the big cats in the Zoological Society's gardens receive adequate supplies of vitamins and trace elements as far as one can estimate, fed as a bulk mix.

2. A possible post-infectious condition: the interesting observation about this is the classical panleucopenia of felines is rarely witnessed as a clinical entity in lions as apart from the other big cats.

3. Some hereditary factor: whilst this is supported by some workers it does not seem to apply in the case of the London lions.

"During the course of the illness in the lion referred to above, both electrocardiograms and electromyograms were carried out. The latter indicated a polyneuritis, but further reports on the histology of the central nervous system are still awaited.

"In an endeavour to investigate the incidence of this disease elsewhere, many authorities all over the world have been contacted and preliminary results indicate that many people in charge of lions experience a very similar condition."

Mr. R. T. W. Fiennes (London): "In supplementation of Mr. Jones's remarks on this condition in lions at the London Zoo and elsewhere, the following result was derived from examination *post-mortem* of the case he mentioned. The affected muscles were pale, but not white. Histologically, fibres were atrophic not dystrophic. The nervous system showed fat and degeneration of neurones in the lateral columns, but not elsewhere, in spite of which sympathetic involvement was not a clinical feature. In the endocrine system, there were pituitary lesions affecting the *pars* posterior and basophil cells of the *pars* anterior; the adrenal cortex was atrophic; thyroid was normal, but parathyroids not examined. The testes were undeveloped and only partially descended. The heart was normal, but the aorta was thickened and showed collagenous degeneration of elastic fibres. The skeletal system also was affected. Bones of the skull showed an osteoporatic condition, but with little deformity except of the perpendicular place of the ethmoid and the turbinates; this was neither a form of rickets nor of osteitis fibrosa ('rubber bone' condition); it resembled the condition that arises in Ca/Ph imbalance. Further lesions were found in the intestinal tract, which may or may not have been associated with the main condition. The small intestine was much thickened due to hypertrophy of the mucous membrane and the villi. This was thought to be associated with the presence of worm larvae deeply embedded in the mucosa; these were probably the larvae of the Belascaris sp., which were present in small numbers in the duodenum. The right side of the liver was fibrotic and atrophic—presumably in association with the intestinal lesions; the left side was swollen, fatty and hyperaemic, in correspondence with a swollen and hyperaemic spleen.

"The lesion of the spinal cord did not correspond with that described by Innes as associated with the migrations of worm larvae.

"The aetiology of the condition is a complete mystery and one of the many problems with which zoo clinicians and pathologists are faced. Others are bone diseases (osteitis fibrosa and rickets in New World monkeys), thyroid diseases in foxes, and cage paralysis in monkeys. Many appear—*a priori*—to be dietary in origin, but do not respond to appropriate treatment. The two papers by Dr. Blaxter and Dr. Walton are most useful in stimulating thought along new lines."

Dr. J. C. Buxton (Sutton Bonington): "I was particularly interested in Dr. Blaxter's film showing, so clearly, the symptoms of muscular dystrophy in calves and I think that the disease may be more widespread than is appreciated. Cases are presented for *post-mortem* examination from time to time but, obviously, clinical diagnosis is difficult.

"Dr. Blaxter has told us how the condition can be treated. Could he give some idea of how long it would take for affected muscle to regenerate and regain its use?

"I believe the muscular dystrophy occurs in fowls, and that in many such cases there is fatal cardiac involvement. Lesions of the skeletal muscles are typically bilateral in birds, as in mammals. May I ask Dr. Blaxter if he has any information on this aspect of the disease?"

Mr. J. G. Brotherston (Moredun): "Scrapie of sheep has been mentioned on several occasions. I was most interested to note that in the myopathies described by Dr. Blaxter and the diseases of muscle in humans described by Dr. Walton, all have shown recognisable changes, gross and histopathological, in accord with the clinical signs seen during life. In the absence of my colleagues, I would like to point out, that in the course of extensive investigations into scrapie at the Moredun Research Institute, it has been found that changes in the muscles are neither widespread nor obvious, in spite of the striking clinical syndrome exhibited by both natural and experimental cases of scrapie, during life."

Mr. A. Brownlee (Compton): "Dr. Blaxter's films showed symptoms in calves affected with myopathy which one would associate with muscle stiffness. I would like to point out that in scrapie, on the contrary, the animal's gait indicates a laxity of muscle movement, which has led to the use of the popular descriptive term 'cuddie-trot.'"

The Replies

Dr. Walton said that he was very interested in the remarks of the speakers from the London Zoo about the disease in lions. If possible, he would like to know a little more about the nature of the electromyographic changes, upon which the diagnosis of polyneuritis was based, because the electrical findings in polymyositis were once regarded as being due to inflammation of the peripheral nerves. There were a great many possibilities with regard to the aetiology if the condition were a polyneuritis. Incidentally, had anybody been able to perform a lumbar puncture on a lion? (*Laughter.*) The so-called acute post-infective polyneuritis was an allergic condition in which the CSF protein was greatly raised, though there was no increase in cells. It would also be of great interest to see the muscle sections from the animals to see whether there were any changes comparable to those in human muscle disease. If there were such sections he would like to see them.

There were a number of neurological changes in humans such as polyneuritis and spinal cord degeneration, which occurred in conjunction with nutritional defects and intestinal changes. Where a blind loop was left after an operation curious biochemical changes might occur, giving rise to macrocytic anaemia, and even sometimes degeneration of the spinal cord.

Stiffness was not a characteristic of human muscular dystrophy. Patients suffering from human muscular dystrophy and polymyositis had weakness of proximal limb muscles which gave the impression of walking stiffly. True stiffness due to the phenomenon of myotonia difficulty in relaxation occurred in only one form of human muscular dystrophy.

His comments about scrapie followed entirely on Dr. Parry's article in *The Lancet*. He had no idea as to the nature of the basic pathological process in human muscular dystrophy. Though much had been learned about the characteristics of muscle fibre degeneration we still knew very little of its essential biochemical cause. As for Dr. Blaxter's statements about cod-liver oil he had never come across any type of muscle disease in human beings which could be attributed to the excessive intake of cod-liver oil.

Dr. Blaxter commented briefly on the points made by Dr. Walton, the first being that familial periodic paralysis in man was associated with a very sudden precipitous fall in the potassium content of the blood leading to the muscles concerned. He did not know that in animals a syndrome which was in any way comparable occurred, but in the calf they could produce, experimentally, a type of paralysis due specifically to potassium deficiency. In such animals the serum potassium fell from the normal 23 mg. to 7 or 8 mg. and as a result a spastic type of paralysis occurred. Paralytic ileus and severe distension which appears comparable with the human condition, was also associated with an abnormally low serum potassium. This could be of some practical interest in so far that low serum potassium sometimes occurred in calves with acute disturbances of the alimentary tract.

Dr. Walton's remarks on the hereditary and irreversible condition in man raised the question of whether there were similar hereditary conditions in animals. In the North of Scotland he and his colleagues had investigated the pedigrees of stock affected by muscular dystrophy and could find no hereditary incidence at all. Furthermore, the diseases in stock could be cured and prevented by dietary changes. Most of the diseases were associated with particular types of husbandry, and their apparent familial incidence merely reflected the common feeding of the herd.

The statements about the lions at the London Zoo were of interest. In experiments that had now been performed with about 15 different species it had been found that the most simple way to produce muscular degeneration was to feed unsaturated fatty acids. There has been some initial difficulty in producing muscular degeneration in this way by feeding cod-liver oil to carnivores but recent work had shown that muscular degeneration could be produced in the cat and the dog. It was the case, of course, as both Mr. Jones and Mr. Fiennes had pointed out, that zoo animals lived in rather abnormal conditions, and both would no doubt be familiar with the fact that at the New York Zoo muscular dystrophy had occurred in a koala bear. That, however, was associated with feeding rather excessive quantities of cod-liver oil. He wondered if there was any possibility of excessive amounts of unsaturated fatty acid getting into the diet of the lions in any way? The amounts would have to be large since the carnivore was less sensitive to unsaturated fat than was the herbivore. Some of the signs appeared comparable to vitamin B_1 deficiency and work on the pig indicated quite clear-cut muscle changes ascribed to B_1 deficiency but, of course, a pig was a pig and a lion a lion!

In experimental cod-liver oil poisoning it had been found that the disease could be prevented comparatively easily by using simultaneously massive amounts of vitamin E—up to 250 mg. daily. The success achieved in attempts to cure the disease after stopping cod-liver oil administration was proportional to the degree to which the animals' musculature was affected. Obviously, if something like half the musculature had undergone an acute degeneration a cure was rather a forlorn hope. Experimentally, cures had been obtained only in animals mildly affected. The success of veterinary surgeons in curing cases of enzootic muscular dystrophy had probably increased because the disease was now recognised much earlier than hitherto, before the maximal muscular damage had taken place.

As to the process of regeneration, even in an acutely degenerated muscle one usually saw histological evidence of regeneration taking place, as had been shown by Dr. Walton's slides of non-hereditary myopathies. By means of straightforward, uncomplicated, vitamin E deficiency and by feeding unsaturated fatty acids, Professor Dam, in Copenhagen, had experimentally produced a myopathy in fowls.

They had already heard during the discussion that while there appeared to be an association between scrapie and the myopathic condition under consideration there was no reason to believe that this was a case of cause and effect. First of all, as Dr. Brownlee had pointed out, the clinical syndrome of scrapie was entirely different from the partial paralysis and weakness of muscular degeneration and, as Mr. Brotherton had said, a comprehensive investigation had shown that scrapie sheep had no myopathic changes in their muscles. Nevertheless, the apparent widespread incidence of myopathy in certain flocks in the south of England represented a challenge to the veterinary profession.

Dr. Wooldridge had asked a question concerning the primary biochemical disturbance in these myopathies which was extraordinarily difficult to answer, or even to start to answer. They now knew a good deal about what occurred inside the muscle cell during the initial stages of the degeneration process. The primary change appeared to be associated with the supply of high energy phosphate bonds to the cell. The change in the creatine phosphate content of the cell in its A.T.P., sodium and potassium content, together with the increase in oxygen consumption both pointed to the primary cause being a dissociation of oxidation from phosphorylation in the cell. One needed to go a stage further back than this before one got to the real cause. As yet is it not known where vitamin E acted, where the unsaturated fatty acids acted or where the genes acted to cause this primary defect in a muscle cell. Work going on in Germany and America implicated vitamin E as a component or activator in the cytochrome C reductase system and further research would help to clarify the situation. The subject was extremely complicated and difficult and so far no concise statement of the biochemical changes could be made.

Oedema Disease in Swine

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THE phenomenally high incidence of oedema disease observed during the immediate 4 to 5 post-war years is no longer evident, having declined to what may now be regarded as a steady or normal incidence rate interrupted from time to time by unpredictable periods of high incidence in different areas. Despite this over-all reduction, the disease may be regarded as one of the major pig diseases in Ireland, and is probably responsible for more deaths over weaning age than any other. In a comprehensive survey of pig losses on 395 Irish farms, Gracey (1955) found that it accounted for 39.6 per cent. of all deaths in weaned and fattening pigs up to 4 months of age. There are also reasons for believing that the incidence may be higher than laboratory records show, because of the difficulty sometimes encountered in establishing a diagnosis based on the examination of single carcases in which the characteristic lesions may be very slight, present in atypical sites only, or completely absent.

Geographical Distribution of the Disease

During the past 7 years our knowledge regarding the geographical distribution of the disease has widened and, in addition to Ireland, Great Britain, Holland, Norway, South Africa, Canada and the United States of America, it now includes France (Hars, 1951), Belgium (Ide & Sierens, 1951), Switzerland (Fey, 1951), Italy (Barei & Binaghi, 1951), Yugoslavia (Zeljko, 1955), Poland (Larski, 1955), Hungary (Erdos *et al.*, 1955), Sweden (Rooney, 1957) and Germany (Köhler, 1957). In view of the present wide distribution of the disease, it would appear reasonable to assume that it probably exists in many other countries where it is either undiagnosed or confused with some other condition.

The purpose of this communication is to record some additional experimental work and observations made by the author and other workers towards solving the aetiology of oedema disease since the Association's Congress was held in Cardiff in 1950.

On the basis of the results obtained from the experimental investigation of the disease together with a study of the naturally occurring condition, the hypothesis was advanced that the disease was a specific toxaemia either originating in the bowel or due to the ingestion of a preformed toxin (Timoney, 1949, 1950). Since no convincing evidence was subsequently published or obtained by the author invalidating the hypothesis, it was decided to subject it to experimental trial. The main prop supporting the hypothesis was the experimental reproduction of the oedema disease syndrome in respect of clinical symptoms and *post-mortem* lesions in a proportion of pigs inoculated intravenously with centrifuged supernatant bowel fluid from naturally occurring cases of the disease (Timoney, 1949, 1950). This finding was subsequently confirmed by Lamont *et al.* (1950), Hudson (1951) and more recently by Sojka *et al.* (1957) and Gitter and Lloyd (1957).

Although a large number of intestinal supernatants from oedema disease cases were used in the experiments made at that time in the experimental reproduction of the syndrome, similar material from only 4 non-oedema carcases was tested for control purposes (Timoney, 1950). From these carcases, 13 pigs were inoculated with a negative result. In view of the small number of control supernatants tested, it was decided to increase the number of control experiments because of the irregularity with which clinical evidence of the experimental disease occurs in pigs inoculated with random specimens from cases of the disease.

Further Control Experiments on the intravenous inoculation of pigs with supernatant fluid from centrifuged small intestinal contents of pigs not affected with oedema disease.

These experiments served two purposes; first, by augmenting the limited number of control experiments already made with intestinal supernatants from non-oedema disease carcases, and second, by ascertaining if such fluid contained a rapid-acting toxic agent. The effects of this agent are not infrequently observed, and often with fatal results, during the course of, and immediately after, the intravenous inoculation of pigs with bowel supernatants from cases of oedema disease. When the effects of this toxic factor were first encountered, it was thought that the toxicity might be due to a very potent oedema disease producing bowel supernatant, but in many of those cases which recovered from the acute symptoms, usually after less than the intended dose had been given, oedema disease did not develop. Furthermore, it never occurred in those cases where toxicity was manifested with small doses and further injection was deliberately stopped to prevent death.

Materials and Methods

Centrifuged supernatant bowel fluid was obtained from 6 sets of intestines from healthy pigs freshly killed at a local bacon factory, and also from 5 store pigs slaughtered at the laboratory affected with a condition resembling Glasser's disease. Intestinal contents from the healthy pigs were extracted with normal saline overnight at 34 to 36° F. before centrifugation at 2,800 r.p.m. for 1 hour.

Dosage

No fixed dose was used, administration being continued until it was considered an adequate volume had been injected for the purposes of the experiment. In those cases where toxicity was of such severity that further administration was deemed unsafe, the injection was discontinued.

Results

No symptoms of oedema disease developed in any of the 9 surviving pigs, nor were lesions of the disease present in the 3 which died.

Toxicity was generally first manifested by reddening of the skin over the snout, ears and eyelids with marked congestion of the conjunctival vessels followed or accompanied by convulsive muscular movements affecting the head and limbs. In the severe and usually fatal cases these were succeeded by a period of apnoea followed by intermittent gasping respirations which generally preceeded death. Vomition and retching movements were frequently noted during the course of inoculation or very shortly afterwards.

In the 3 fatal cases the *post-mortem* findings were characterised by intense congestion of the gastro-intestinal tract with haemorrnage into the contents, particularly noticeable in the colon and small intestine, excessive fluidity of intestinal contents, pallid liver and kidneys, scattered haemorrhages in otherwise bloodless lungs and marked haemorrhages in the left ventricular endocardium. In one carcase, there was oedema of the wall of the gall bladder. A summary of the results of the experiments is given in Table I.

Discussion

None of the inoculated pigs which survived developed oedema disease, thus lending further support to the opinion that the oedema disease toxic factor is a specific factor associated with intestinal supernatants from oedema disease carcases.

The presence of a rapid-acting toxic factor which produces symptoms and *post-mortem* lesions similar to those produced by some bowel supernatants from oedema carcases has been demonstrated in bowel fluid from non-oedema carcases. It, therefore, appears reasonable to assume, that the rapid acting toxic property of some bowel supernatants from oedema cases is due to some extraneous toxic factor other than that responsible for the symptoms and lesions of oedema disease. No attempt was made to determine the nature of the factor, but the rapidity with which symptoms develop suggests that it is of small molecular size and, from limited observations, it would appear that no immunity is developed against it. The symptoms and lesions, however, would suggest the action of a histamine-like substance.

Subjection of the hypothesis that the disease is a specific toxaemia either originating in the bowel or due to the ingestion of a preformed toxin to experimental test.

The alternative or second limb of the hypothesis referring to the ingestion of a preformed toxin was chosen for examination first, because on the results obtained would largely depend the validity of the first limb of the theory.

Experiments to determine if the gastric contents of affected carcases contain the oedema disease producing factor.

It was concluded that if the oedema disease producing toxic factor or agent—irrespective of its nature—was ingested or formed in the stomach in the same state as that in which it is present in the bowel contents, it should be possible to demonstrate its presence by the intravenous method of inoculation of fluid expressed from the gastric contents, or possibly by the more simple administration of this fluid to pigs by means of the stomach tube.

It was considered that these experiments would be of assistance in defining the extent of the field of inquiry to be covered in a search for the source of origin of the oedema disease producing factor.

TABLE I

THE INTRAVENOUS INOCULATION OF PIGS WITH CENTRIFUGED SUPERNATANT FLUID FROM INTESTINAL CONTENTS OF PIGS NOT AFFECTED WITH OEDEMA DISEASE

Pig number	Wt./lb.	Dose/ml. supernatant fluid	Source of material	Dilution of contents with normal saline		Result
				Saline : Contents		
1	25	32	Factory	1	5	Toxic symptoms at 25 ml. Injection discontinued at 32 ml. Survived.
2*	29	6·5	"	"	"	Toxic symptoms at 5 ml. and very marked at 6·5 ml. Injection discontinued. Died within 2 hours.
3*	25½	3·5	"	"	"	Severe toxic symptoms at 3 ml. Injection discontinued at 3·5 ml. Died within 3 hours.
4	31	40	"	"	"	No toxic symptoms observed. Survived.
5	34	6	"	"	"	Severe toxic symptoms at 6 ml. Injection discontinued. Survived.
6	28	37	"	"	"	No toxic symptoms observed except salivation towards completion of inoculation. Survived.
7	26½	30	"	"	"	No toxic symptoms observed. Survived.
8	34½	26	Laboratory	Undiluted		Severe toxic symptoms at 26 ml. Injection discontinued. Survived.
9	45	28	"	"		Severe toxic symptoms at 28 ml. Injection discontinued. Died within a few minutes.
10	29	10	"	"		Toxic symptoms at 5·5 ml. Injection interrupted for 1 to 2 minutes and then continued until 10 ml. administered. Survived.
11	37	30	"	"		Marked increase in respirations at 20 ml. Injection interrupted for 1 to 2 minutes and a further 10 ml. administered. Survived.
12	34	30	"	"		No toxic symptoms observed. Survived.

* Pigs 2 and 3 were inoculated with supernatant fluid obtained from the same carcase.

Experimental Methods and Materials

Experiment 1

The gastric contents of a carcase, the intestinal contents of which were shown to contain the oedema disease producing factor by pig inoculation, were mixed with 400 ml. of normal saline and extracted for 48 hours at 34° to 36°F. The contents were squeezed between several layers of muslin and the 490 ml. of expressed fluid obtained were administered through a stomach tube to a pig (30 lb.) previously fasted for 28½ hours.

Experiment 2

One pig (38 lb.) received through the stomach tube 800 ml. of expressed fluid obtained from the pooled gastric contents of 3 carcases, which had been mixed with 400 ml. of normal saline and extracted for 3 days at 34° to 36°F.

Results

The results of the foregoing few experiments were negative and in keeping with those previously recorded, where large quantities of alimentary contents were fed to pigs with a similar result. In experiment No. 1 the pig proved susceptible to experimental oedema disease 15 to 18 days after dosing. The susceptibility of pig in experiment No. 2 was not tested. Since further experiments along the above lines were not likely to yield decisive results it was decided to use the more critical method of intravenous administration.

Intravenous Experiments

The plan adopted was to test by intravenous inoculation not only the gastric but also the intestinal contents from each of a series of carcases in which were characteristic lesions of oedema disease. This involved the use of at least 2 pigs for each experiment 1 for gastric and the other for intestinal fluid. Thus, it was possible in each experiment to make a direct comparison of the oedema disease producing properties of the respective fluids originating from the same carcase. This procedure was considered likely to give greater significance to the results than if a straight series of gastric contents only were examined.

Materials and Methods

The gastric and intestinal contents were obtained from carcases originating from 18 outbreaks of oedema disease occurring on the same number of premises.

Preparation of Gastric and Intestinal Supernatants

The entire stomach contents were firmly compressed between 2 to 4 folded layers of muslin by hand, and the expressed fluid collected and centrifuged at 2,800 r.p.m. for 1 hour. The centrifuged supernatant fluid was collected and stored at 34° to 36°F.

In many cases the intestinal contents were run out and diluted according to their amount and consistency with varying volumes of normal saline. In instances when the yield of contents was likely to be small or the bowel appeared empty, it was perfused with a known volume of normal saline which was massaged through its entire length and the resulting mixture collected. In other cases, the bowel was run out and perfused afterwards with a known volume of saline, the perfusate being added to the first collection. All contents containing saline were extracted overnight at 34° to 36°F. and centrifuged the following day.

The volume of gastric supernatant fluid recovered on centrifugation ranged from 25 ml. to 180 ml. and the intestinal from 22.5 ml. to 230 ml. The intestinal contents were extracted with varying volumes of saline in all cases except those from carcase 3.

Dosage. For convenience the volume of supernatant inoculated is expressed as a percentage of the total volume of supernatant recovered in each case. In some experiments 2 inoculations were given to the same animal within an interval of 24 hours.

The experimental pigs were of the Large Irish White breed and from 8 to 10 weeks old. As far as it was practicable to do so, litter mates were selected for inoculation with materials from the same carcase.

Inoculations were given into an ear vein under light chloroform anaesthesia.

A Summary of the results is given in Table II.

Discussion

The results obtained under the conditions of the foregoing experiments failed to provide evidence that the oedema disease toxic factor was present in the gastric contents of pigs which died of oedema disease. The conclusion drawn from these experiments was that the toxic factor is neither ingested nor formed in the stomach in its active or toxic state. Accordingly, an intoxication resulting from the ingestion of a preformed bacterial toxin was eliminated as a cause of the disease; likewise, the ingestion of other toxic agents originating in or contaminating the food, such as phytotoxins or other toxic substances of a vegetable or chemical nature were also excluded. There remained, however, the theoretical possibility of the toxic factor being either ingested or formed in the stomach in an inactive or non-toxic form and subsequently activated to the toxic state through enzyme action on reaching the bowel. This alternative explanation was ignored for the time being in favour of the more simple and direct interpretation of the experimental results.

Specific Toxaemia Originating in the Bowel

The results of the previous experiment were accepted as localising the seat of origin of the toxic factor to the intestine. Attention was, therefore, concentrated on the first limb of the hypothesis, namely, that the disease is a specific toxaemia originating in the intestine. The salient points in the accumulated clinical and experimental evidence supporting this were as follows:—

Clinical

(1) The explosive nature, rapid course and abrupt termination of outbreaks.

(2) The absence of a temperature reaction in nearly all cases of the disease.

TABLE II.

RESULTS OBTAINED FOLLOWING THE INTRAVENOUS INOCULATION OF PIGS WITH CENTRIFUGED SUPERNATANT FLUIDS DERIVED FROM THE GASTRIC AND INTESTINAL CONTENTS OF 18 OEDEMA DISEASE CARCASES

Carcases						
Gastric Supernatant Fluid				Intestinal Supernatant Fluid		
Origin of fluids	Number of pigs inoculated	Per cent. of total volume inoculated in ml.	Result	Number of pigs inoculated	Per cent. of total volume inoculated in ml.	Result
Carcase number						
1	1	20+28	No symptoms of O.D. Lived	1	21+25	O.D. Died. Confirmed P.M.
2	1	100	" " " " "	1	59	Died overnight. O.D. not confirmed.
				1	41	Died overnight. O.D. confirmed P.M.
3	1	86	" " " " "	1	67	Died overnight. O.D. confirmed P.M.
				1	33	O.D. Died. Confirmed P.M.
4	1	98	" " " " "	1	32	O.D. Died. Confirmed P.M.
5	1	98	" " " " "	1	32	Normal.
6	1	48	" " " " "	1	17	O.D. Destroyed. Confirmed P.M.
7	1	49	" " " " "	1	47	Symptoms of O.D. Recovered.
	1	51	" " " " "	1	53	Normal.
8	1	100	" " " " "	1	56+44	Normal.
9	1	33	" " " " "	1	65	O.D. Died. Confirmed P.M.
				1	35	O.D. Died. Confirmed P.M.
10	1	100	" " " " "	1	100	O.D. Destroyed *in extremis*. Confirmed P.M.
11	1	15	Very toxic injection stopped. Lived.	1	56	Indefinite illness for 3 days. Lived.
12	1	35	Died overnight P.M. Negative for O.D.	1	88	Died overnight. O.D. confirmed P.M.
	1	35	No symptoms of O.D. Lived			
13	1	100	" " " " "	1	95	O.D. Died. Confirmed P.M.
14	1	59+38	" " " " "	1	39+61	Normal.
15	1	48+52	" " " " "	1	48+52	O.D. Died. Confirmed P.M.
16	1	100	" " " " "	1	97	O.D. Died. Confirmed P.M.
17	1	97	" " " " "	1	81	O.D. Died. Confirmed P.M.
18	1	50	Died within 5 hours. Negative for O.D. on P.M.	1	100	Destroyed 8 days after inoculation P.M. negative for O.D.

O.D. = Oedema Disease.
P.M. = *Post-mortem* Examination.
\+ = 24 hours interval between inoculations.

(3) The failure of the disease to spread from pig to pig in natural outbreaks of the disease.

(4) The frequency with which the best thriving pigs are first affected.

Experimental

(5) Failure to reproduce the disease by parenteral and non-parenteral routes with various tissues and body fluids from naturally affected animals or carcases.

(6) The negative results obtained on bacteriological examination of freshly killed carcases from both natural and experimentally produced cases of the disease.

(7) The experimental reproduction of the oedema disease syndrome by the intravenous inoculation of centrifuged bowel fluid from naturally occurring cases of the disease.

(8) Failure to reproduce the disease by the inoculation of centrifuged supernatant bowel fluid from pigs not affected with oedema disease.

(9) Failure to transmit the disease from experimental cases to other pigs by the intravenous inoculation of blood, bowel supernatant fluid or by contact.

(10) Failure to demonstrate the oedema disease toxic factor in the gastric contents of affected carcases.

(11) The relatively large inoculum required to reproduce the disease particularly with saline extracted contents.

(12) The short period which may elapse in some cases between inoculation and the appearance of symptoms and also the frequent occurrence of deaths within 24 hours with diagnostic lesions on *post-mortem*.

(13) The reproduction of the oedema disease syndrome with filtrates of supernatant intestinal fluid.

While the above evidence could not be regarded as definitely excluding a viral origin, the weight of evidence was totally against such a conception having regard to our present knowledge of virus diseases.

The conclusion drawn from clinical and experimental observations was that the naturally occurring disease was caused by the absorption into the system of a specific toxic factor formed in the bowel whereas the experimentally induced syndrome represented poisoning of the experimental pig by the intravenous inoculation of the unabsorbed

portion of the toxic factor present in the bowel contents of the naturally affected pig at time of death. Consideration of a non-living agent of a specific nature likely to cause the disease indicated the probability of the toxic factor being of the nature of a bacterial toxin, this decision being influenced to some extent by the fact that specific toxaemias of bacterial origin originating in the bowel are well-established entities in sheep. Some thought had been given to the possibility of a toxaemia originating from a non-bacterial toxic product produced in the bowel, but was dismissed as not conforming with the epidemiology of the disease. Experiments were, accordingly, initiated to see whether any experimental evidence could be obtained in support of a specific toxaemia of bacterial origin originating in the bowel.

Influence of temperature on the oedema disease toxic factor in centrifuged supernatant intestinal fluid

Since most bacterial exotoxins are thermolabile it was decided to determine the effect of heat on the oedema disease producing capacity of centrifuged supernatant bowel fluid.

Materials and Methods

Centrifuged supernatant bowel fluid was obtained from 2 outbreaks of the disease. In each case, this consisted of neat centrifuged supernatant fluid mixed with centifuged supernatant obtained from the intestinal contents extracted overnight with normal saline at 34° to 36°F. and then centrifuged at 2,800 r.p.m. for 1 hour.

In the first experiment, the supernatant from one outbreak was divided into 3 equal volumes of 25 ml. each, 2 of which were heated in unplugged test-tubes 2.5 cm. in diameter in a boiling water bath for 15 minutes. The coagulum which formed was thrown down by centrifugation and the combined supernatants (32.2 ml.) inoculated intravenously into a pig. The remaining unheated supernatant was inoculated into a control pig.

In the second experiment, a portion of the supernatant fluid from the second outbreak was heated in 15 ml. quantities in unplugged similar test-tubes for 15 minutes at 60°, 65° and 70°C. respectively. Pigs were inoculated with the heated preparations and controls with unheated supernatant fluid.

Experimental pigs were of the Irish Large White breed and varied in weight from 26½ to 36½ lb. Those used in the first experiment were litter mates, as were those used in the second experiment, except one in the control group. For other details of the experiment see Table III.

Discussion

Although only a small number of experimental pigs were used the results were clear cut and, pending further experiments, were tentatively regarded as indicating that the oedema disease toxic factor is comparatively susceptible to heat—a feature common to most exotoxins.

The potency of the 2 supernatants tested was shown by the rapidity with which the animals developed symptoms and the acute course the disease followed. Under the conditions of the experiment it would appear that the toxic factor was destroyed or inactivated between 60° and 65°C. The delayed symptoms in the pig inoculated with the preparation heated at 60°C., when compared with the control animals, was suggestive of a decrease in the toxicity of the preparation induced by the heat treatment.

Post-mortem examination of the pigs which died or were killed *in extremis* revealed marked oedema of the stomach wall and colonic mesentery in each case.

Experiments to determine if centrifuged supernatant bowel fluid from oedema disease carcases is antigenic

TABLE III

INFLUENCE OF TEMPERATURE ON THE OEDEMA DISEASE PRODUCING CAPACITY OF CENTRIFUGED SUPERNATANT BOWEL FLUID WHEN HEATED IN A WATER BATH AT BOILING POINT 70° C., 65° C. AND 60° C. FOR 15 MINUTES.

	Pigs inoculated	Weight lb.	Dose/ml. of supernatant fluid	Result
Experiment I.				
Boiling point	1	27½	32·2	Remained normal.
Unheated	1	33	25	Marked inco-ordination of all limbs, 16 hours after inoculation. Died within following 24 hours.
Experiment II.				
70° C.	1	34	14·3	Remained normal.
65° C.	1	29	14·3	Remained normal.
60° C.	1	26½	14·3	Normal for 24 hours followed by inability to rise. Muscular tremors and skin haemorrhages present. Killed *in extremis* 42 hours after inoculation.
Unheated	1	32	15	Unable to rise, running limb movements. Died 16 hours after inoculation.
„	1	36½	14·2	Unable to rise, muscular tremors, hypersensitive, squeal hoarse. Killed *in extremis* 19 hours after inoculation.
„	1	32½	10	Unable to rise, running limb movements. Killed *in extremis* 24 hours after inoculation.

This was regarded as a critical test, because if the disease were of the nature of a specific toxaemia originating in the bowel, it should be possible to demonstrate that the serum of pigs immunised against bowel supernatant fluid from natural cases of the disease would protect experimental pigs against the oedema disease toxic factor. That the preparation might be antigenic received some support from clinical evidence, in that as previously recorded (Timoney, 1950), the occurrence of secondary outbreaks of the disease in previously affected litters was very rarely observed, suggesting the development of an immunity among the surviving members of the litter.

Methods and Materials

Two pigs A and B were immunised at different times. Pig A was a store pig 13 weeks old and had been housed at the laboratory for some weeks. It had never shown any clinical evidence of oedema disease. Pig B had suffered from a severe form of oedema disease when about 12 weeks old. At time of immunisation it was approximately 15 months.

Immunisation Process

Pig A. The immunising antigens were obtained from 3 different outbreaks of oedema disease. Four inoculations were given over a period of 78 days. The first 2, consisted of alum precipitated material derived from formalinised (0.5 per cent.) diluted centrifuged supernatant fluid, to which a solution of alum potash had been added to give a concentration of 2 per cent. in the mixture. This material represented the pooled supernatant fluid of 4 carcases from 1 outbreak. The third and final inoculations comprised untreated potent supernatant fluids originating from separate outbreaks. The potency of the preparation used for the first 2 inoculations could not be determined because of the presence of a lethal toxic factor referred to earlier in this paper. In consecutive order, the quantities administered were 30 ml. intraperitoneally, 20 ml. intramuscularly, 25 ml. intravenously and 35 ml. intravenously, and the intervals between the inoculations were 35, 21 and 22 days. The pig was bled out 7 days after the final inoculation and the serum preserved with 0.5 per cent. phenol.

Pig B. For this pig, immunisation material was obtained from 3 separate outbreaks of the disease. The immunisation process extended over 4½ months, during which period it received 6 inoculations (250 ml.) of alum precipitated formalinised supernatant bowel fluid by the intraperitoneal and intramuscular routes, and 2 intravenous inoculations of 20 ml. and 50 ml. respectively of untreated centrifuged supernatant bowel fluid intravenously. The only immunising preparation tested for potency prior to inoculation was the supernatant fluid used in the final inoculation. It was very potent when tested on pigs around 33 lb. in weight causing paralysis within 18 hours. The pig was slaughtered 8 days after the final inoculation and the serum preserved with 0.5 per cent. phenol.

Bowel supernatant from 5 different sources was used in the first 9 series of experiments, while in the tenth series a pooled supernatant from 3 other outbreaks was employed. In all cases except 2, the intestinal contents had been extracted with saline.

Normal pig serum for control purposes was obtained from a pig of bacon weight and of unknown history slaughtered at the Dublin abbatoir.

Mixtures of bowel supernatant and serum were well mixed and incubated at 37° C. for 20 to 30 minutes prior to inoculation. Where bowel supernatant was used without serum it was also incubated.

The experiments were made over 10 different occasions and litter mates of comparable weights were used for most of the experiments. Experimental pigs were of the Irish Large White breed.

The principals varied in weight from 18.5 to 32.5 lb. with an average weight of 27.1 lb., and the controls from 17 to 35 lb. with an average of 26.7 lb.

All inoculations were given intravenously into an ear vein under light chloroform anaesthesis.

For further particulars see Table IV.

Results

Principals. Of 25 pigs in this group, 24 survived the inoculation and showed no symptoms of oedema disease. One pig died within 3 hours after inoculation from an acute toxic condition of unknown cause.

Controls. Of 24 pigs in this group, 22 died (5 were destroyed when *in extremis*), of which 21 were affected with oedema disease. The remaining pig (685) died 6 hours after inoculation and, although no gastric or mesenteric (colon) oedema was present, death may have been due to acute oedema disease, since there was well-marked oedema of the wall of the gall bladder and an area of oedema around the portal-gastric lymph node and along the serous aspect of the lesser curvature of the stomach.

Of the 2 surviving pigs (604 and 612) 1 survived the inoculation with no evidence of oedema disease and the other developed a mild form of the disease from which it recovered.

Discussion

The results were unexpectedly good. The criterion of protection was taken as the absence of clinical symptoms together with survival. The protective properties of both sera showed that the immunising preparations were antigenic. As the material for immunisation was not prepared from bacteria-free filtrates, it cannot be stated unequivocally that the toxic oedema factor in the bowel supernatant was the only factor concerned in the production of protective substances in the sera of the immunised pigs. The inclusion of a number of intestinal micro-organisms would be inevitable even with more highly centrifuged preparations than were used in these experiments.

Despite this objection, and having regard to the available experimental evidence on the disease, the results were interpreted as showing that the sera A and B possessed neutralising bodies which prevented the development of the experimental oedema disease syndrome and that the toxic oedema factor was of the nature of a toxin. The weight of evidence being

TABLE IV

SERUM PROTECTION EXPERIMENTS WITH PIG SERA A AND B.

	Principals				Controls			
Experiment number	Pig	Bowel supernatant	+ Serum	Result	Pig	Bowel supernatant	+Normal serum	Result
1	592	10 ml.	+10 ml. A	Survived	589	10 ml.	—	O.D. Died
1	593	10 „	+10 „	„	599	10 „	—	„ Destroyed
1	594	10 „	+10 „	„	591	10 „	—	„ Died
1	595	10 „	+10 „	„	—	—	—	—
2	608	12 „	+12 „	„	603	12 „	—	„ Died
2	609	12 „	+12 „	„	604	12 „	—	„ Recovered
3	614	20 „	+20 „	„	612	20 „	—	Survived
3	616	20 „	+20 „	„	613	20 „	—	O.D. Died
4	625	23 „	+23 „	„	624	23 „	—	„ „
5	680	15 „	+15 ml. B	„	679	15 „	—	„ „
5	682	15 „	+15 „	„	681	15 „	—	„ „
5	684	15 „	+15 „	„	683	15 „	—	„ „
5	686	15 „	+15 „	„	685	15 „	—	„ ? Died
6	689	20 „	+20 „	„	688	20 „	—	„ Destroyed
7	691	20 „	+20 „	„	690	20 „	—	„ Destroyed
7	693	20 „	+20 „	„	691	20 „	—	„ Died
8	697	15 „	+15 „	Died within 3 hours	696	15 „	+15 ml.	„ Destroyed
8	699	15 „	+15 „	Survived	698	15 „	+15 „	„ Died
9	701	10 „	+10 „	„	700	10 „	+10 „	„ „
9	703	10 „	+10 „	„	702	10 „	+10 „	„ „
9	705	10 „	+10 „	„	704	10 „	+10 „	„ „
10	751	20 „	+10 „	„	754	20 „	+10 „	„ Destroyed
10	752	20 „	+10 „	„	756	20 „	+10 „	„ Died
10	753	20 „	+10 „	„	757	20 „	+10 „	„ „
10	755	20 „	+10 „	„	758	20 „	+10 „	„ „

Normal Serum = Serum obtained from pig about 12 st., wt., slaughtered at abattoir. O.D. = Oedema disease.

completely against the disease being viral in origin, is now seemed reasonable to conclude that the toxic oedema factor was bacterial in origin.

Microscopical Examination of Stained Smears of Intestinal Contents

Influenced by the fact that the most notable exotoxin producers are largely confined to the gram-positive group of micro-organisms, stained smears were made from different levels of the small intestine of a number of carcases but failed to reveal any undue predominance of this group of organisms. The findings were quite contrary to those described in entero-toxaemia in sheep. Moreover, centrifuged supernatant fluids from cultures of the *Clostridium welchii* types B and E, and also from *Cl. oedematiens* and *Cl. septicum*, while toxic and lethal for pigs on intravenous inoculation did not produce the characteristic symptoms and lesions of oedema disease.

Normal Intestinal Filtrate Cultures

It was considered that a medium consisting of a sterile filtrate of small intestinal contents from normal pigs might prove suitable for the development of the toxic oedema disease factor when seeded with intestinal contents from a freshly killed carcase of the disease.

A number of these cultures were made, incubated aerobically, and tested for toxicity at various periods of incubation by the intravenous inoculation of centrifuged supernatant cultural fluids in varying dosage (14 to 54 ml.) into 15 pigs.

Encouraging initial results were obtained, in that symptoms associated with the early stage of oedema disease—such as slight inco-ordination of the posterior limbs, accompanied in some cases with muscular tremors and intermittent convulsive body jerks (hiccough-like movements)—were observed in some of the inoculated animals. Since these symptoms did not progress in the first animal inoculated, it was killed after 4 days with evidence of very slight oedema in the cardiac submucosa; no other lesions were present. Of the succeeding 14 inoculated pigs, 7 were slaughtered within 20 to 24 hours after inoculation, previous inspection having indicated that they were likely to recover; 4 of these showed evidence of oedema in the gastric submucosa or gastric submucosa and colonic mesentery. The lesions were very slight except in 1 pig, in which there was oedema of the cardiac zone and gastric diverticulum approximately ¼ inch in thickness. Of the remaining 7 pigs, 4 survived with no symptoms of oedema disease and 3 died, 1 in 68 minutes and the second 16 hours after inoculation. Both showed *post-mortem* findings similar to those seen in acute toxic poisoning referred

to in the early part of this paper. The third pig was unable to rise, and was making running movements with all limbs when seen in the morning—20 hours after inoculation; it was found dead 2 hours afterwards. *Post-mortem* examination revealed slight oedema of gastric wall and colonic mesentery and marked oedema of the terminal portion of the rectum.

Further Experiments with Intestinal Cultures

Following on the previous experiments, bacterial isolations were made from blood agar and plain agar plates sown with contents from different levels of the small intestine. Haemolytic and non-haemolytic colonies of gram-negative bacteria which were the predominant types were inoculated into normal pig intestinal filtrate, glucose broth, liver fusion broth, and Hartley's broth and the centrifuged supernatant fluids injected in varying dosage into pigs. None of the pigs developed symptoms of oedema disease; and apart from a few which died within a few hours after inoculation with lesions similar to those seen in acute toxic poisoning, all the pigs survived. The results were disappointing and less encouraging than those obtained with the supernatants from mixed cultures seeded direct from the bowel as in the previous cultural experiments.

In the light of the foregoing experiments and the inconsistent and generally negative results, consideration was given to the possibility that for adequate toxin production special media requirements might be necessary, the determination of which might take a considerable time. Consequently, in the event of such a possibility, it was realised that the absence of a potent culture supernatant under the conditions of the previous experiments would not necessarily eliminate a cultural growth as being of no significance in the causation of the disease.

Further examination of the problem, as to ways and means of surmounting the difficulty, suggested an indirect approach through the immunisation of pigs with different bacterial isolations from the bowel, and testing the protective effects of the respective sera when mixed with potent bowel supernatant fluid.

Bacteriological Examination of Small Intestinal Contents

From a field case of the disease which had died about 1 hour previously, the small intestine was divided into approximately 5 equal sections (1 to 5) starting from the duodenal extremity. Three blood agar plates were sown in series with diluted intestinal contents from each section and incubated aerobically overnight. Haemolytic colonies showing β-type haemolysis were present on all the primary plates in rapidly increasing numbers as one proceeded from the most anterior to the most posterior section of the bowel, except in Section 2, all 3 from which were negative (probably due to an error in technique). They were sparse on the primary plate from the first section, innumerable on the primary plates from the third and fourth sections, and so numerous on the primary and secondary plates from the ileal or fifth section that three-fourths of each plate was completely haemolysed. Microscopic examination of the colonies showed them to be gram-negative rods resembling *Escheridia coli* in morphology. Several of the colonies were subcultured on plain agar and nutrient broth and retained for further study.

Similar isolations were made from the fresh carcase of another outbreak of the disease, in the ileal contents and perfused bowel fluid of which, they represented about 50 per cent. of the colonies. As a matter of interest, it was then decided to ascertain if there was any serological relationship between the haemolytic organism isolated from this carcase and the serum of pig B referred to in the preceding serum protection experiments, which had been immunised with bowel supernatant fluid. Tube agglutination tests were made, first with 1, and then with 3 other phenolised (0.5 per cent.) antigen suspensions prepared from cultures originating from 4 separate colony isolations and incubated for 24 hours at 37° C. The suspensions were agglutinated to a titre of 1/25,600 (end point not determined). A normal serum control (abattoir pig) agglutinated to a titre of 1/400. Further control tests were made on 19 sera obtained from old sows slaughtered at a local bacon factory. Nine of these gave titres of 1/100 of which 4 reached a titre of 1/800.

Protection experiments with serum of pig (739) immunised with haemolytic gram-negative organism (E. coli) *isolated from the intestinal contents of an oedema disease carcase*

It was originally planned to immunise a number of pigs with different bacterial isolations from the bowel and test the respective sera for protective properties against potent bowel supernatant fluid. However, in view of the very high agglutination titre obtained with pig serum B and the haemolytic gram-negative organism subsequently identified as *E. coli*, and having regard to the results of the other control tests and its prevalence in the bowel, it was decided to immunise a pig with the organism and test its serum for protective properties against potent bowel supernatant fluid.

Preparation of Antigen for Immunisation Purposes

The organism was cultured in 3 × 200 ml. vols. of liver infusion broth and in 2 × 200 ml. vols. of Hartley's digest broth. The flasks were inoculated from a 24-hour growth on an agar slant (fifth subculture) incubated for 72 hours at 37° C. and then formalin added to give a concentration of 0.5 per cent. They were re-incubated for a further 4 days; removed from incubator, and a 10 per cent. solution of alum potassium sulphate added to give a concentration of 2 per cent. in the mixture. They were then removed to the refrigerator and after 10 to 11 days, shaken, and the contents centrifuged for 10 minutes at 2,800 r.p.m. in capped bottles, and most of the supernatant fluid removed, sufficient being left to make a fairly thick suspension of the deposit for inoculation purposes. Purity and sterility tests were made at appropriate stages throughout the process.

Immunisation of Pig for Production of Serum

A pig No. 739 about 45 lb. weight, with no previous history of having had oedema disease, was selected for immunisation. It had been purchased a month previously and was in good thriving condition.

The immunisation process extended from January 24th, 1956, to July 24th, 1956, a period of 6 months, during which a total of 128 ml. consisting largely of centrifuged precipitated cultural deposit was injected. The inoculations were given at irregular intervals. Eighty millilitres were injected intraperitoneally in 4 successive doses of 20 ml. within a period of 34 days. After a rest interval of 63 days, 48 ml. were given intramuscularly in doses varying from 8 ml. to 20 ml. within a period of 79 days. Six days after the previous injection, a final inoculation was administered intravenously of 5 ml. of a dense suspension in saline of a 24-hour agar growth equal in opacity to twice tube No. 9 of Brown's opacity standard. A systemic reaction was evident the next morning consisting of reddening of the skin, inappetence, and a temperature of 106.4° F. Streptomycin was administered and the pig was normal in 48 hours. It was destroyed 7 days after the last inoculation and the serum preserved with phenol (0.5 per cent.). *Post-mortem* examination revealed some slight fibrous adhesions in the peritoneal cavity and an indurated abscess in the gluteal region of each hip about the size of a walnut. The carcase was in excellent condition and well nourished.

Experimental Methods

From among several supernatants tested for potency only 4 were suitable for experimental purposes as judged by a preliminary potency test. They were obtained from outbreaks of the disease which occurred on 4 separate premises. In each case the intestinal contents were extracted with saline. The supernatants were not pooled, the experiments being made from time to time as potent preparations became available and not more than 1 experiment was carried out on the same day. The supernatants were used as follows: the first supernatant in experiment 1, the second in experiments 2, 3, and 4, the third in experiments 5 and 6, and the fourth in experiment 7. The volume of supernatant fluid in each case was approximately the same as that which proved potent on the preliminary potency test. Normal serum for the control experiments was obtained from a pig of bacon-weight killed at the Dublin abattoir. It was preserved with 0.5 per cent. phenol. The serum and supernatant fluids were well mixed and maintained at 37° C. for 20 to 30 minutes in the incubator prior to inoculation.

All inoculations were given into an ear vein under light chloroform anaesthesia. The principal and control pigs in each unit were injected 1 immediately after the other and returned to the same pen. Experimental pigs were of the Irish Large White breed and varied in weight from 24 to 37 lb. The average weight was 27.1 lb. Litter mates were used in each experiment.

Results

All the pigs (principals) which had received a mixture of bowel supernatant and pig serum 739 were normal the day after inoculation, except pig 777 which had a slight scour but otherwise was feeding and behaving normally. The scour had ceased the following day.

All the control pigs showed symptoms of oedema disease and died, except pig 765 which was killed when in an advanced stage of the disease and unable to rise.

The characteristic symptoms of swelling of the eyelids and staggering gait followed by paralysis of the limbs were evident in every case. In some animals, muscular tremors and intermittent muscular spasms (body jerks) in addition to alteration in the tone of the squeal or grunt were also observed. In one animal, skin haemorrhages (flea-bite-like in appearance) were present on the inside of the thighs and abdomen. Urine samples from 3 carcases reduced Benedict's solution. In the remaining 4 it was negative in 2 instances and in 2 carcases the bladder was empty.

The following are the periods which elapsed between inoculation and the appearance of diagnostic symptoms and death, together with the salient lesions of oedema noted on *post-mortem* examination:—

Pig 765 showed symptoms on the second day after inoculation and was killed on the fourth day. Slight oedema of cardiac submucosa of stomach.

Pig 774 showed symptoms on the second day after inoculation and died the same day. Moderate oedema of cardiac submucosa of stomach.

Pig 776 showed symptoms on the second day after inoculation and died the same day. Marked oedema of cardiac submucosa of stomach.

Pig 778 showed symptoms on the first day after inoculation and was found dead the following morning. Marked oedema of cardiac submucosa of stomach and oedema of colon and caecum.

Pig 783 showed symptoms on the second day after inoculation and was found dead on the morning of the fourth day. Marked oedema of cardiac submucosa of stomach.

Pig 785 showed symptoms on the first day after inoculation and was found dead on the morning of the third day. Marked oedema of cardiac submucosa of stomach and slight oedema of the colonic mesentery.

Pig 790 showed symptoms on the first day after inoculation and died on the second day. Slight oedema of cardiac submucosa of stomach and colonic mesentery.

Discussion

While only 7 experiments were made the results were clear-cut and were accepted as demonstrating the specific protective effect of pig serum 739. The results were equally as decisive as those obtained in the protection experiments with pig sera A and B. Incidentally, the experimental results were taken as disproving that oedema disease is of viral origin.

As the experiments were simply of a pilot nature and the potency of the serum unknown, it was decided to use fairly large doses of serum for mixing with the bowel supernatant fluid. The complete absence of symptoms in the serum-protected pigs suggests that smaller doses of serum might have been used with a similar effect. On the other hand, the potency of the respective supernatant bowel fluids used when judged by previous experience in the experimental

TABLE V
PROTECTION EXPERIMENTS WITH PIG SERUM 739

Principals						Controls				
Experiment number	Pig number	Wt./lb.	Bowel supernatant	+ Serum 739	Result	Pig number	Wt./lb.	Bowel supernatant	+ Normal serum	Result
1	766	24½	20 ml.	+10 ml.	Survived	765	29	20 ml.	+10 ml.	O.D. Destroyed
2	773	24	25 „	+10 „	„	774	24	25 „	+10 „	„ Died
3	775	24	25 „	+10 „	„	776	24	25 „	+10 „	„ „
4	777	24½	24 „	+10 „	„	778	25	24 „	+10 „	„ „
5	784	30½	20 „	+10 „	„	783	30	20 „	+10 „	„ „
6	786	26	22 „	+10 „	„	785	37	22 „	+10 „	„ „
7	789	28	17 „	+ 7 „	„	790	29	17 „	+ 7 „	„ „

O.D. = Oedema disease.

production of the oedema disease syndrome probably did not contain more than 1, or in some instances possibly 2, lethal pig doses, for pigs of the weight range used in the experiments.

The significance of the results lay in demonstrating through the protective effect of the serum the immunological relationship of the immunising antigen to the oedema disease toxic factor, thereby indirectly incriminating the *E. coli* used as antigen as a source of origin of the oedema disease toxic factor produced in the bowel. The protection afforded was attributed to neutralisation of this factor by an antitoxic factor to factors present in the serum.

Experiments with frozen and thawed extracts of E. coli *isolated from oedema disease carcases*

Erskine, Sojka and Lloyd (1957) showed that frozen and thawed extracts of strains of haemolytic *E. coli* isolated from the intestines and mesenteric glands of field cases of oedema disease when inoculated intravenously into pigs produced a syndrome indistinguishable from oedema disease in the majority of the inoculated animals. Using the same method, with some variations, these findings have been confirmed by the author with extracts prepared from 7 strains of haemolytic *E. coli* comprising 2 serological types. Two of the strains were isolated from the small intestine and 5 from the colon of carcases originating on 7 different premises.

At various times 14 pigs were inoculated with extracts, of which 5 were in an experiment to be described later. Eight received extracts from 1 strain prepared on 4 occasions, and 6, individual extracts obtained from the same number of strains. The doses of extract injected were 12 ml. and 15 ml. and the pigs varied in weight from 27 lb. to 63 lb. Each pig received 1 gramme of streptomycin intraperitoneally at time of inoculation.

Of the 8 pigs inoculated with extracts from the same strain, 1 died in 22 hours being found *in extremis* on the morning of the first day following inoculation, 7 developed typical symptoms of oedema disease of which 6 died from the second to the third day after inoculation, and 1 was destroyed on the fifth day of illness—when showing signs of recovery. In the remaining 6 pigs, each of which received an extract prepared from a separate strain, there was considerable variation in the severity of the symptoms manifested. Two pigs showed inco-ordination of limb movements 4 hours after inoculation and died in 11½ hours; 2 developed characteristic symptoms of oedema disease, 1 of which died on the second day, and 1 was destroyed on the fourth day after inoculation when in the stage of recovery, and 2 showed slight swelling of the eyelids associated with a moderate degree of inco-ordination of movement in 1 case and an occasional sway of the hind limbs in the other from which they recovered.

Post-mortem examination of all the pigs which died on the second or third day after inoculation—including the 1 which died in 22 hours—showed oedema of the cardiac submucosa; in 1 case it was associated with oedema of the last 4 to 5 inches of the rectum and in 2 with oedema of the colonic mesentery. In the 2 pigs which died approximately 11½ hours after inoculation, the lesions were of an acute type characterised by a haemorrhagic condition of the bowels with haemorrhage into the interior, marked reddening of the fundic and pyloric zones of the gastric mucosa, multiple haemorrhages in the lungs and endocardium, oedema of the gall bladder, and marked excess of peritoneal fluid with numerous fibrin threads. In 1 carcase there was also slight oedema of a portion of the colonic mesentery and some oedema of the interlobular connective tissue of the lung. In neither carcase was there any evidence of oedema of the stomach wall. *Post-mortem* examination of the 2 pigs which were killed in the recovery stage revealed no oedema lesions although 1 of them was still affected with complete paralysis of the fore limbs and partial paralysis of the hind limbs at time of slaughter.

Experiments to determine if pig serum 739 will protect pigs against the experimental oedema disease syndrome produced by an extract prepared from a strain of E. coli

The protective property of pig serum 739 having been previously demonstrated against the oedema disease toxic factor in bowel contents of affected carcases, it was considered important to ascertain if it would also protect pigs against the oedema disease syndrome produced by an extract of *E. coli*.

Methods and Materials

Two extracts of a strain of *E. coli* originally isolated on December 13th, 1955, from the intestinal contents of an oedema disease carcase were used. The same strain had been used in the immunisation of pig 739. The extracts were prepared from a 72-hour growth on 1.9 per cent. agar containing 0.1 per cent. glucose in Roux flasks, washed off with 20 ml. of sterile saline and rapidly frozen at −78° to 79°C. and thawed 10 to 12 times at 37°C. in rapid succession. The suspensions were centrifuged at 2,800 r.p.m. for 90 minutes and the supernatant fluids removed and kept frozen until required.

Four pigs, litter mates, were used for testing the first extract, and 6 pigs from various litters for the second extract.

Mixtures of serum and extract were incubated at 37° C. for 20 to 30 minutes prior to inoculation by the intravenous route. Each pig received 1 g. of streptomycin intraperitoneally at time of inoculation.

Results

All the experimental pigs were very dull and listless for several hours after inoculation.

Controls. Pig 841 showed marked excitability when seen 20 minutes after inoculation, manifested by running round the pen and losing control of its hind limbs on turning. During progression it exhibited a very rapid stringhalt action of both hind limbs. It eventually developed paralysis of all limbs, swelling of the eyelids, and alteration of voice, and was destroyed on the fifth day of illness when it had partly recovered control of the hind limbs. *Post-mortem* did not reveal any lesions of oedema disease.

Pig 837 died 22 hours after inoculation. When seen at 16 hours the squeal had altered and it was unable to rise. No swelling of the eyelids was present. *Post-mortem* examination revealed marked oedema of the stomach wall and colonic mesentery.

Of the 3 remaining control pigs, 2 showed symptoms of oedema disease on the second day after inoculation, 1 of which died the same day and the other the following day. The third pig showed symptoms on the first day after inoculation and died on the second day. All 3 pigs showed marked oedema of the stomach wall (cardiac zone) associated in 1 case with slight oedema of the colonic mesentery.

Urine samples from 4 carcases reduced Benedict's solution in 2 cases. No urine was present in 1 carcase.

Heart-blood cultures made from 4 of the carcases gave negative results.

Principals. All the pigs in this group behaved normally, fed 24 hours after inoculation, and continued to do so.

Discussion

The significance of the results obtained was that they showed that the same serum which had protected against oedema disease producing bowel supernatants, also protected against extracts of a strain of *E. coli* originally isolated from the intestinal contents of a natural case of the disease. Based on the results of these and the previous protection experiments with serum 739, the conclusion seems unavoidable that the same oedema disease toxic factor is present in both bowel supernatant fluids and in extracts of haemolytic *E. coli* isolated from the intestines of oedema cases.

In these experiments the extracts were prepared from the same strain of *E. coli* as that used for the production of the protective serum and therefore were of the same serological type. Further experiments are necessary to show if serum produced against 1 serological type will protect against an extract of a different serological type. It may well be that the toxin formed is common to all serological types.

E. coli in Oedema Disease

The first published reference to haemolytic *E. coli* in oedema disease was made by Schofield and Davis (1955) who commented on their abundance in faecal

TABLE VI

PROTECTION EXPERIMENTS WITH PIG SERUM 739 AGAINST AN EXTRACT OF A STRAIN OF *E. coli* ISOLATED FROM THE INTESTINAL CONTENTS OF AN OEDEMA DISEASE CARCASE

Principals					Controls				
Pig Number	Weight in lb.	Extract of *E. coli*	+ Serum 739	Result	Pig number	Weight in lb.	Extract of *E. coli*	Normal + serum	Result
828	62	15 ml.	+7·5 ml.	Survived	829	53	15 ml.	+7·5 ml.	O.D. Died
830	66	15 „	+7·5 „	„	831	63	15 „	+7·5 „	„ „
836	36½	12 „	+6 „	„	837	35·5	12 „	+6 „	Died. O.D. confirmed P.M.
838	37·5	12 „	+6 „	„	839	40·5	12 „	+6 „	O.D. Died
840	34	12 „	+6 „	„	841	38·5	12 „	+6 „	„ Destroyed

O.D. = Symptoms of oedema disease.
P.M. = *Post-mortem* examination.

cultures from cases of the disease as suggesting "a relationship between the organism and the disease." In the same year, Gregory recorded that the predominant organism isolated from the small intestine from 5 different outbreaks of oedema disease was a β-haemolytic coliform organism, whereas, in a similar examination of 14 non-oedema carcases, these colonies were not observed, except in 1 case in which they were very few in number. Sojka, Erskine and Lloyd (1957) in a comprehensive study of a large number of haemolytic *E. coli* strains isolated from intestinal contents and mesenteric lymph nodes of affected carcases, refer to their isolation in 1951 by Hudson, Huck, Shand, and Buntain and in 1953 by Gitter. Lemcke *et al.* (1957) have also recorded the constancy of β-haemolytic *E. coli* in gut oedema of baby pigs.

The author's attention was first drawn in 1955 to the prevalence of haemolytic *E. coli* in the intestinal contents when screening the small intestine of a carcase with a view to making bacterial isolations for immunisation purposes. Coliform organisms had, however, been isolated in 1948 by the author and his colleagues from the mesenteric lymph nodes of some carcases during the course of routine bacteriological examinations, but were discarded at that time as of no aetiological importance. Since the protective value of the serum of pig 739 immunised with an *E. coli* strain was established, haemolytic colonies of *E. coli* have been isolated generally in large numbers from intestinal material, especially from the large intestine of every case where cultural examinations have been made. In many cases, particularly in cultures from the colonic contents, the plates resembled a pure culture of the organism.

Sojka *et al.* (1957) have shown that the vast majority of *E. coli* strains examined by them from oedema disease carcases comprise 2 serological types. Preliminary agglutination tests made by the author with the serum of a pig immunised with 1 strain have shown that a number of the strains so far isolated and tested fall into 2 groups: those which are agglutinated to a very high titre and those which give a very low reaction. Serological examinations of a number of these strains by Sojka *et al.* (1957) have shown that they correspond to the 2 main serological types observed by these workers. It is highly probable that the same sero-types prevail in all countries where oedema disease occurs. What significance different sero-types will have in the development of biological products devised for the prevention and treatment of oedema disease has yet to be revealed.

Summary

(1) Supernatant bowel fluid from pig carcases not affected with oedema disease failed to produce oedema disease on intravenous inoculation into pigs.

(2) The presence of a non-specific toxic factor was demonstrated in supernatant bowel fluid from non-oedema disease carcases.

(3) Experiments failed to demonstrate the oedema disease producing factor in stomach contents of oedema disease carcases.

(4) The oedema disease producing capacity of bowel supernatant fluid from oedema disease carcases failed to produce the oedema disease syndrome when heated at boiling point, 70° and 65° C. for 15 minutes.

(5) Pigs inoculated with a mixture of serum from pigs immunised with supernatant bowel fluid from field cases of oedema disease and supernatant bowel fluid obtained from similar cases of the disease failed to develop oedema disease.

(6) Pigs inoculated with a mixture of serum from a pig immunised with a strain of haemolytic *E. coli* isolated from the intestine of a field case of oedema disease and supernatant bowel fluid from a naturally affected carcase failed to develop oedema disease.

(7) Pigs inoculated with the same serum as used in the above experiment (No. 6) when mixed with extracts of *E. coli* isolated from the intestine of an oedema carcase failed to develop oedema disease.

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THE SPEAKER'S INTRODUCTION

Mr. Timoney, in introducing his paper, said his first duty was to thank the organising committee of the Congress for the invitation to present a paper on Oedema Disease of Swine. It was an honour and privilege he appreciated very much. The title might have been more aptly styled "Further Advances in the Study of Oedema Disease" since it was largely concerned with experimental work done on the disease since 1950. The paper could have been longer and more detailed, but then it would probably have made tedious reading except for those who had a research interest in the subject. It was, therefore, decided to restrict it to those salient aspects of the work not only

of interest to the research worker but also to veterinary surgeons engaged in general practice.

His interest in the disease first started in 1947, and at that time, and in the immediately successive years, there was a general clamour as to its nature, the cause, and how it could be prevented. It was a case of conducting investigations with a pistol at one's head, under which conditions it was extremely difficult to conduct research successfully. There was little doubt that if, following the experimental reproduction of the disease in 1949 and 1950 a sufficient number of adequately trained personnel had been made available to study the disease, a solution to the problem would have been obtained some years ago.

Briefly, the various stages of the work dealt with in the paper comprised:—

(1) Additional control experiments with bowel supernatant fluid obtained from non-oedema disease cases.

(2) Subjection of the hypothesis formulated on the basis of previous work—that the disease is either due to a specific toxaemia originating in the bowel or due to the ingestion of a preformed toxin—to experimental test.

(3) Failing to demonstrate the oedema disease-producing factor in gastric contents, experiments were made to determine:—

(a) the effect of heat on the toxicity of oedema disease-producing bowel supernatant fluid, and

(b) to ascertain if oedema disease-producing supernatant fluid was antigenic as determined by protection tests with sera of pigs immunised with supernatant bowel fluid.

(4) Experiments on bacterial isolations from the small intestine of oedema disease carcases.

(5) Immunisation of pig with a haemolytic bacterial isolation (*E. coli*) from the bowel of an affected pig, and testing the protective effect of its serum against supernatant bowel fluid from oedema carcases.

(6) Testing the protective effect of the same serum against oedema disease-producing extracts prepared from a strain of haemolytic *E. coli* isolated from a field case of oedema disease.

The Opener

Mr. M. K. Lloyd, in opening the discussion, said that at the Congress in 1950, the author, as an opener to the discussion on a paper presented by Professor Lamont and his colleagues entitled "Some Diseases of Pigs," presented details of an exhaustive series of experiments designed to elucidate the cause of oedema disease. His results provided a sound basis for the subsequent work that had been performed by himself and others. The entero-toxaemia theory which he put forward as a rational conclusion to his experimental results had now been established on a firm basis as a result of the work he described in the paper. This evidence must convince even the most sceptical of the validity of his ideas on the aetiology of that condition.

With regard to the incidence of the disease, the author had drawn attention to the survey conducted by Gracey in Northern Ireland in 1955. A survey by the Ministry of Agriculture Veterinary Investigation Service from March, 1955, to February, 1956, indicated a somewhat similar state of affairs in England and Wales, and oedema disease appeared to be one of the four most common causes of post-weaning losses. Out of 1,322 such losses, material from which was submitted to Veterinary Investigation Centres for diagnosis, 13 per cent. were attributable to oedema disease. It was exceeded in incidence in that age group by gastro-enteritis (21.6 per cent.) and pneumonia (18 per cent.).

Now that evidence had been produced that an infective agent might be responsible for causing that disease, it was useful to look at the pattern followed by outbreaks to see if the infective nature could be detected. In general that aspect of the natural disease did not seem particularly evident. However, Barron and Howell in 1949 reported that in some outbreaks deaths occurring in recently purchased pigs were followed a week later by deaths from oedema disease in the home-bred pigs. It seemed reasonable to interpret those observations by assuming that the predisposing factors were already present on the farm, and the imported pigs brought the infection with them. That kind of history did not appear to be common, but one such outbreak was recorded at Weybridge. Again, this time on the experimental side, Mr. Timoney produced some evidence that healthy pigs occasionally went down with oedema disease a week to 10 days after having been introduced into pens of affected pigs. As a general observation on that point, it seemed that the factors predisposing pigs to infection by the organisms were a very important part of the picture, and might tend to obscure those features which characterised the distribution of many infections.

The results of the experiments described in the paper to determine the origin and nature of the toxic agent found in the bowel supernatants from oedema disease cases were confirmed in some aspects by experiments on a more limited scale performed at Weybridge: thus (1) supernatants from the intestinal contents of healthy pigs were found to be inactive; (2) supernatants from stomach contents also failed to produce the oedema disease picture; (3) heating potent bowel supernatants at 100° C. inactivated them.

A point of great importance in the paper was the evidence showing that on the basis of antigenic tests, the toxic agents in the bowel supernatants appeared to be identical with those found in the frozen and thawed extracts of *E. coli* strains from oedema disease cases. Those results were perfectly clear cut and put the idea of *E. coli* strains being an essential factor in oedema disease on a firm footing. Results at Weybridge using serum prepared from live organisms and also from potent bowel supernatants had so far failed to demonstrate protection, passive or active, against the effects of bowel supernatants. The method of serum production was different from that used by the author and passive protection tests were all carried out by injecting pigs with serum a few hours prior to challenge, whereas the author used an *in vitro* neutralisation. The inference was that the techniques were not adequate to detect the antigenicity which had clearly been shown to be present by the author.

The table (shown as a slide) illustrated some serological results. It indicated the results of serotyping of the first 200 strains examined. All were strongly haemolytic on 5 per cent. sheep blood agar plates with the exception of 6 strains. None of those 6 were typable with the sera used. From the results it could be seen that 3 serotypes emerged as the commonly recovered types E4, E57, E68, and they covered 87.5 per cent. of the strains. Using frozen and thawed extracts of each of those 3 strains, oedema disease symptoms and lesions were produced experimentally. The remaining 11 sera used all appeared to represent less common types, and before they could be accepted as being implicated in oedema disease, further evidence must be produced, as in the case of E38 when, again, frozen and thawed extracts reproduced the condition. Only 6.5 per cent. of strains were not typable using all 14 sera, again demonstrating the degree of uniformity to be found in those isolates. The uniformity of serotypes had been observed in several clinical conditions associated with *E. coli*, for example, infantile gastro-enteritis of babies and white scour in calves. Dr. Williams Smith had kindly examined a number of the strains using phage typing and had found that all E4 types were lysed by a single phage.

E. coli strains from a variety of pathological conditions from various species were examined at Weybridge and early in the serological investigation of strains from oedema disease it was found that there was considerable overlapping with strains isolated from gastro-enteritis cases in pigs, as could be seen from the table. However, E4 appeared more specific for oedema disease and G7 for gastro-enteritis. Serotypes E57 and E68 appeared to be equally common in association with both conditions. E68 was of particular interest since recently there had been cases reported of haemorrhagic gastro-enteritis complicated by the presence of typical oedema disease lesions in which that serotype was isolated. A paper on the strains isolated from pathological conditions in pigs was in preparation.

The author had given a list of those countries in which oedema disease had been reported, and in that connexion

strains isolated from oedema disease cases in France, Italy, Norway, and the United States had been examined at Weybridge, and from each of those countries the same serotypes had been found as those occurring commonly in this country. So far, no reports of the disease occurring in Australia had been recorded, and enquiries made to several veterinarians in that country indicated that it had not so far been diagnosed there. It would be interesting to see whether the associated serotypes did, in fact, occur in Australian pigs.

As indicated in a previous report, it was found that haemolytic organism was confined to the intestinal tract and associated lymph nodes, where it could be isolated often in apparently pure growth. Those concerned at Weybridge were particularly fortunate in finding a farm close at hand where oedema disease occurred in almost every litter reared, at approximately one week after weaning. The litters were followed up by examination of rectal swabs from before weaning to some time after outbreaks subsided. Thus it was possible to follow closely the time of appearance and disappearance of the organism in the intestinal canal of the pigs, and also its distribution and relation to disease outbreaks.

Six consecutive litters had been studied, and it was found that the haemolytic organism (E4 serotype) always made its appearance about 4 days following weaning, only a small percentage being present at first, but rapidly building up in a day or two days, becoming in many cases apparently pure on direct culture of swabs onto blood agar. A proportion of those pigs died usually on the fourth day following the initial appearance of the organism in the faeces. All were typical cases of oedema disease, and in all almost pure growth of the E4 serotype was found in the intestines and often in the mesenteric lymph nodes. In the pigs remaining unaffected the organisms gradually subsided, and only a few were detectable 10 days after its first appearance. During those studies other pigs on the farm including the dams of the litters used were examined from time to time, but in no case could that serotype be detected.

On that farm a phthalylsulphathiazole B.P. trial was conducted in several litters, oral dosing of 0.3 g. per kg. per day for variable periods—3 to 10 days—was used, given in the feed. Litters were divided at, or soon after, weaning, into treated and untreated groups and rectal swabbing instituted. In all cases the drug prevented the appearance or caused the disappearance of the organism. Control groups behaved as indicated previously. Throughout the trial no pig died which was not showing the organism in the faeces. Only one pig died in the treated groups —during the night following the first dose of the drug. Out of 4 control groups deaths occurred in 3.

In those litters where treatment was only for 3 or 4 days, the serotype reappeared in most animals about 3 to 4 days after cessation of treatment, and among those pigs one death occurred which was a typical case, and again the type organism was recovered in almost pure growth at the *post-mortem* examination.

It appeared from that small trial that in the case of outbreaks due to the E4 serotype, phthalylsulphathiazole treatment, if instituted early enough, would confer protection during the period of medication. The drawbacks to the practical use of that drug prophylactically were, of course, that outbreaks must be anticipated, and since most appeared sporadically such anticipation, in most cases, was not possible. The reappearance of the organism after treatment was also a drawback.

Passing to more speculative aspects of the disease, it was perhaps important to discuss both the nature and mode of action of the toxic agents involved and also the predisposing factors which led to the establishment of the syndrome in the presence of the specific organism.

Little could be said with assurance about the toxic agents involved, beyond the fact that they could be produced by certain serotypes of *E. coli*, and were apparently antigenic and heat labile. The isolation in pure or highly active form of those agents would greatly facilitate a full understanding of their mode of action.

Perhaps the most important aspect of the disease was the question of predisposing factors. There were various indications that those factors were of major significance. Thus, at Weybridge the feeding of live cultures of the specific serotypes, on many occasions, to recently weaned pigs had invariably resulted in no observable effect. The organisms disappeared rapidly from the faeces when the feeding of cultures was discontinued. Again, in outbreaks the in-contact pigs which remained healthy might harbour in their faeces large numbers of the specific bacteria. It seemed, therefore, that one must account both for the establishment of the organism in the gut, and also, once established, to account for the production and absorption of sufficient of the toxic agent to produce disease. Probably the majority of outbreaks occurred shortly after weaning—7 days after being very common. To-day it is common practice to wean piglets at 2 weeks old and rear them on "sow milk substitute," and on that system of management, again, many outbreaks occurred a week later. Presumably, the changes at weaning, possibly feeding changes, led to changes in the intestinal flora, and during the change-over period before a new balance was established, the intestines provided a suitable nidus for the particular organisms involved in the disease.

With regard to practical approach to the condition in the field, it was the nature of the condition to appear suddenly and to disappear equally quickly, deaths often being confined to one day. Thus treatment would be of limited value and treatment trials, unless adequately controlled, might appear to give beneficial results because of the tendency for rapid disappearance of the disease.

Preventive measures, if successful, would obviously be preferable. The use of antibiotics, vaccines, and sera held some promise, however, when the predisposing factors involved were more completely understood. Then, perhaps, a more rational approach to the problems could be made, and simple, cheap, and effective control methods established.

The General Discussion

Professor Lamont (Belfast) said that it was fitting that he should be the first person to take part in the general discussion on Mr. Timoney's paper as Mr. Timoney had opened the discussion on the paper which he and his colleagues gave at Cardiff. He congratulated Mr. Timoney on the results achieved and admired his persistence in his work on this very baffling disease. In Belfast they had also worked with these coliform cultures which were examined by their colleagues in Weybridge and found similar to the ones with which they had reproduced the disease. One sentence which Mr. Timoney had used deserved special mention, namely, if a team had been put on to the solving of this problem after the Cardiff Conference he was quite sure that the problem would long since have been solved. He could not agree more. At Stormont they were so involved with routine advisory work, research work took a very secondary place. Fortunately Mr. Erskine of the Weybridge team had worked at Stormont and had kept them fully informed of the developments. He would like to say that bowel oedema was a very mysterious disease and many strange things occurred in connexion with it. He still thought there were many pieces of this jig-saw puzzle which had to be sorted out and fitted into place. He congratulated the Weybridge workers and Mr. Timoney on their work.

Mr. M. A. Clay (Framlingham) asked whether it was agreed that incidence of lesions in the gastric mucosa was increasing against those found in the colonic mesentery, and whether this might be associated with the identification of two serological types of *E. coli*?

Mr. W. E. Parish (Weybridge) said: "I wish to congratulate Mr. Timoney in the presentation of his paper and the results of his many years of patient research into the aetiology of oedema disease of swine.

"There is no doubt that a toxic agent from certain strains of *Bacterium coli* does cause an oedematous condition in pigs, and there is strong evidence for believing that this is the cause of oedema disease in the field. Both he and Mr. Lloyd have stressed the importance of predisposing causes, admitting, however, that there is no clear-cut evidence of the nature of these factors in pigs.

" In order to investigate the mechanism of the pathogenicity of *Bact. coli* in animals, experiments were undertaken on rabbits and fowls using strains of *B. coli* isolated from, and pathogenic for, those species. Though a wide range of conditions may be produced by strains of this organism, these remarks will be confined to those aspects related to oedema disease. A preliminary warning is necessary that no results obtained from work on one species can be directly transposed to apply to another.

" The *Bact. coli* are part of the normal flora of the alimentary tract. Large oral doses of pathogenic strains or their toxic components given to normal animals, do not cause disease, but if anything disturbs the normal relationship between the host and this natural flora, these organisms may set up septicaemia or toxaemia. The factors so far investigated have been derangement of normal peristalsis, change in the *p*H of the lumen contents, changes in the consistency of the diet, experimental depression of mucosal growth in young animals by means of antibiotics, and sudden fluctuations in environmental temperature. Each and all will aid penetration of the *Bact. coli* organisms, or of the toxic extract following their fragmentation. One common sequel to all these experimental interferences is the disruption of a layer containing muco-polysaccharide elements lying over the cuticular strated border of the villi. The significance of this is still under investigation.

" A toxic fraction may be found in the alimentary canal of fowls affected with an enteritis caused by *Bact. coli*. In the controls we found a parallel phenomenon to that described by Mr. Timoney, in that the intravenous injection of the supernatant fluid of the contents of the small intestine of about 65 per cent. normal, clinically healthy birds resulted in immediate moderate to severe shock (of which, incidently, we have taken a cinematograph record), but I disagree with Mr. Timoney that it is due to the introduction of ' a histamine-like substance.' For although histamine is very stable it is usually quickly broken down in the body, even the luminal contents have histaminase activity. It is possible that cells damaged during the processing of the supernatant will release histamine, but I suggest a more likely explanation is that peptides obtained from the contents, on intravenous injection release histamine from the cells of the injected animal which causes shock.

" Furthermore we must not forget that we are working with an endotoxin, and in sufficient amounts it may produce a generalised Shwartzman reaction after a single intravenous injection as described by several independent workers, and which may easily be mistaken for other phenomena.

" The finding by Mr. Timoney of smaller numbers of his pathogenic strain of *Bact. coli* anteriorly and more posteriorly in the small intestine also agrees with our findings in the fowl. We believed this to be associated with the concentration of actively phagocytic elements of the reticulo-endothelial system. Injection of particulate dyes showed a massive uptake anteriorly and very little posteriorly. In further experiments we demonstrated (a) that reticulo-endothelial flock potentiated the lethal power of the endotoxin; (b) that *Bact. coli* organisms phagocytised by their cells soon degenerated, therefore more organisms survived in the posterior portion of the gut than in the phagocytic elements.

" Both speakers made reference to the perplexing problem in the field where oedema disease suddenly appears on some farms and affects a few litters before disappearing, whereas on others it may persist for a long time. Mr. Lloyd has described the results of the examination of faecal swabs on some farms where the disease occurs, and the finding of strains of *Bact. coli* associated with those capable of producing oedema disease. This has some analogy to our experiments where small groups each of 5 to 10 animals were kept together and to which was added a carrier-excretor animal. We had found that certain carrier animals harboured the organism within the body on *post-mortem* examination, mostly in the gall bladder or bone marrow, and which were not excretors of this organism during life. Other animals either permitted the establishment of a specific strain of *Bact. coli* within the alimentary tract, or continually supplied the lumen with organisms from some other site, and became excretors. When such animals were added to a group, the pathogenic or type organism could be isolated from the faeces of about 75 per cent., but after a short time it was no longer possible to isolate this organism, though it was still being disseminated by the excretor.

" Finally we have made attempts, without much success, to extend our knowledge of the disease caused by the *Bact. coli* and to determine the mechanism whereby the pathogen causes disease and death. We have found that it is possible to precipitate out all the protein from a sterile extract of the organisms and show that it is still toxic."

Mr. F. G. Clegg (Sutton Bonington) said: " I am interested in the morphological changes produced in the bowel by varying diets, and especially those produced by the long-term supplementation with antibiotics.

" The pronounced thinning of the wall of the small intestine and the resulting reduction of its total weight in supplemented animals is a feature of antibiotic feeding and is largely unexplained. Antibiotics are known to have a pharmacological effect on the peristalsis and tone of the small intestine, and it may well be that the reduced or more irregular peristalsis, during the period of rapid growth of the gut, allows the development of this thinned small intestine.

" Kimbel (1956), working at Erlangen, has found that there was a very noticeable slowing down of the rate of passage of a contrast medium in the upper alimentary tract of rats after the rats had received chlortetracycline for 26 days. The contrast medium would persist in the stomach and duodenum for a considerably longer time than in untreated rats.

" Andersen, working at Copenhagen, has described the more widespread distribution of coliform bacteria in pigs which have received penicillin orally. It was possible in penicillin-treated pigs to isolate these bacteria from the stomach, duodenum, and anterior part of the small intestine, whereas in controls the coliform organisms were generally found in the lower small intestine only.

" I consider that this persistence of organisms in the anterior part of the small intestine resulting from the reduced tone of the alimentary canal, is of considerable importance. The study of morphological changes produced by diets may be very important in an understanding of why potentially pathogenic organisms become established in the bowel, and this peculiar action of antibiotics may be very useful in giving a key to this question."

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Professor W. I. B. Beveridge (Cambridge) asked whether Mr. Lloyd could give any information on the sensitivity to antibiotics of the different serotypes of *E. coli* associated with oedema disease?

Mr. O. V. Gunning (Acle) said: " Pig keepers are notoriously bad feeders of water to pigs. In this age of high nutritional feeding is it not possible that lack of water is an important predisposing cause? As a practical pig keeper myself, I make it a practice that the pigs always have water available."

The Replies

Mr. Timoney, in reply, said that anything he had done in connexion with the disease had been done solely for the profession and in the interests of the pig breeder and feeder, and he wished to take this opportunity of thanking those veterinary surgeons who assisted him in procuring material for experimental purposes. He thanked Mr. Lloyd for his kind remarks on opening the discussion and greatly appreciated the valuable contributions made by him and his colleagues at Weybridge in their recent work on the disease. To Professor Lamont and the other speakers he also wished to extend his thanks for the way they received his paper. It was not easy to reproduce the disease at will in the laboratory, and consequently its investigation was time-consuming and required considerable patience

and perseverance. A further disadvantage was that in the present state of our knowledge all experiments had to be undertaken on pigs and these were not always easy to procure when required for experimental purposes.

With regard to the frequency of oedema of the cardiac zone as compared with the colonic mesentery he had, so far, not examined his *post-mortem* records with that object in view, but his impression was that it was more commonly observed in the stomach wall than in the colonic mesentery.

Although clinical and experimental observations strongly suggested the presence of some non-specific factor or factors which predisposed the pig to the disease, nothing as yet was known about the nature of the factor or factors involved. Change of environment and change of feeding were often cited as precipitating factors although, in many outbreaks of the disease neither of these changes were reported to have occurred. Furthermore, the small pig breeder generally sold his pigs shortly after weaning and at a period when most cases of oedema disease occur, thus making assessment of the influence of changes in environment or feeding on the occurrence of the disease more difficult. Whether the recent very interesting findings of Bullen and Scarisbrick on the rôle played by changes in the diet, in the experimental reproduction of enterotoxaemia in sheep, could be applied to oedema disease, was difficult to say, but they did suggest that research along similar lines might be undertaken for the elucidation of the predisposing factors in oedema disease. The quantity of food eaten would appear to be a factor of some significance since it was almost invariably the best pig in the litter which was first affected. It was a disease which intimately associated with weaning, although not exclusively confined to weanlings.

In reply to the question as to whether the feeding of certain antibiotics to pigs predisposed to the condition, he could only say that the vast majority of pigs in which he encountered the disease had not received feeding-stuffs containing antibiotics.

The effect of the "annoyance" or extraneous toxic factor encountered in some bowel supernatants on inoculated pigs suggested the action of a histamine-like substance, and he appreciated the comment that this might be a release product resulting from the action of some primary agent acting on the tissue cells. That this might be of the nature of a peptide was interesting, but if so, it was difficult to explain the marked variation in the toxicity of different preparations.

No information was available to the author as to whether *E. coli* types isolated from oedema disease cases were associated with mastitis in cows. Clinical evidence strongly indicated that resistance was conferred in the majority of instances on the surviving in-contact members of a litter following an outbreak of oedema disease. In those cases where rapidly occurring successive cases of the disease appeared in an outbreak it was assumed that insufficient time had elapsed for immunity to develop in the in-contacts.

It was true that the disease was less prevalent now than during the immediate post-war years. Many people took the view that this was due to the use of better feeding-stuffs. Another factor was that the pig population during the war years was at a very low figure, but in the immediately succeeding years pig production became very profitable resulting in a sudden increase of what might be regarded as a highly susceptible pig population. The distribution throughout pig stocks of *E. coli* types associated with oedema disease might be much wider than was presently realised and it would be interesting to learn what proportion of sows had protective substances against oedema disease in the colostrum. On account of the unpredictable nature of the disease immunisation of the pregnant sow might offer a practical solution where early weaning was practised. When potent sera were made available they should be of assistance in protecting in-contact pigs and, possibly, for the treatment of clinical cases in the early stages of the disease when given intraperitoneally, or where conditions were suitable, intravenously.

Mr. Lloyd, in reply, said it was interesting to hear from practitioners about their experience of condifions in the field.

With regard to the *Bact. coli* strains, on the whole they tended to be non-haemolytic, and as far as one could see there was no relationship between them in oedema disease; but that picture might change when more had been examined. It was interesting to hear about the successful results of treatment with *Bact. coli* serum.

So far as the question of antibiotic sensitivity was concerned, a number of strains had been examined for antibiotic sensitivity and there did not appear to be any relationship with serotype, and it was possible to reduce the resistance of antibiotics in the strains.

Collateral Hazards from Crop Spraying

BY

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MY right to speak on the hazards of crop spraying derives only from the fact that I was Chairman of the Working Party set up by the Minister of Agriculture and Fisheries in July, 1950, with a request that it " make recommendations for the promotion of the safety of workers in the agricultural use of substances which are toxic or harmful to human beings; and in particular to advise on the recommendations on this subject made in the Report of the Gowers Committee on Health, Safety, and Welfare in Non-industrial employment " (Report, 1951). Our advice on this subject has since been embodied in legislation. This task completed, my Working Party was reactivated by the Ministry of Agriculture and the Secretary of State for Scotland, to consider " the possible risks from the use in agriculture of toxic substances on the agricultural product and the stored product," and, given that protective measures appeared desirable, to make recommendations of their form to the Ministers concerned. The report of this part of our deliberations was published in 1953, under the title " Toxic Chemicals in Agriculture: Residues in Food." We were then reconstituted a third time, and asked to consider the possible risks " to the natural flora and fauna of the countryside from the use in agriculture of toxic substances, including the possible harmful effects for agriculture and fisheries " (Report, 1953). If I stand before you now as the author of a paper on the whole of this complex subject, I do so without any pretensions of being an expert in the subject, or of having something new to say. My knowledge derives partly from the evidence which was brought before my Working Party from a variety of expert sources, and partly from the fact that I have also had the privilege of serving as the first Chairman of the Interdepartmental Committee which was set up by the Government, after the presentation of our second report, to advise Departments first on the risks to the consumer and operator which arise from the use of toxic substances on agricultural products and in the storage of food, and second on the risks to wild life. As a member of this Inter-departmental Committee, I have had the benefit of a first-hand and general view of the problems which emanate from this important field of agricultural practice.

The title to which I have been asked to speak is " Collateral Hazards from Crop Spraying." The direct hazards constitute the specific purposes for which toxic substances have to be used in order to limit waste in various farming operations. Modern techniques of this kind have little place in the farming practice of peasant communities where neither the relative cost of agricultural labour nor violent unrest about standards of living yet constitute immediate social or political problems. In more advanced countries, chemical weed-killers, fungicides, insecticides, rodenticides, artificial fertilisers, sheep dips, and so on are a complementary part of a vast array of other scientific practices whose purpose is to increase the yields and profitability of agricultural operations. All these techniques reflect the fact that the more advanced a country is socially and industrially, the lower the proportion of its labour force that is engaged in agriculture, and, at the same time, the greater, in general, the volume of its agricultural production. A consequence of this form of social and technological revolution is that the farmer inevitably becomes an applied geneticist, or an applied chemist, or even a mechanical engineer. The pace of this technological revolution in agriculture is not likely to be stayed.

The use of chemicals on farms, of course, represents no new principle; practices such as liming and manuring reach far back into the past. With the rapid advance of chemical industry, however, the farmer is being increasingly bombarded with new preparations for more and more specific purposes. Most of the chemicals used in agriculture are toxic in certain circumstances, but the dangers of the long-established ones are usually recognised, and can be guarded against. The popular interest which is now shown in the collateral toxic effects of the chemical treatments used to treat livestock, growing crops, and stored food, is largely due to the post-war introduction of organic pest killers with which we are very much less familiar than we are, say, with such things as arsenical compounds.

Technological progress always entails new social risks. Aircraft crashes; death on the roads; radiation hazards; even the changing spectrum of poliomyelitis, seem to be inevitable concomitants of social progress. But whereas the agricultural worker of, say, the 17th century would have felt that he had only himself to blame for any hurt which he may have suffered in the course of his work, his modern counterpart is convinced that the State should bear the responsibility for the new hazards that arise as a consequence of modern agricultural practice.

Another concomitant of social progress is a more humanitarian, or perhaps one should say a more articulate sense of the new dangers which technological developments bring to the fauna and flora of the countryside. Fifty years ago hardly anyone protested against the deliberate destruction of an animal species in some distant part of the world. At an earlier stage, probably no one protested against the decimation of the wild animals which once lived in this country. To-day our social conscience is very much alive to these happenings.

I do not propose in this paper to consider the risks which the farmer, farm-worker, or spraying contractor runs in using toxic chemicals. Over recent years a number of fatalities bear witness to the dangers

entailed in the use of preparations like DNC, and to the wisdom of the statutory orders which regulate the use of these substances, so as to obviate the consequences of misunderstanding, carelessness, or stupidity. Instead, what I propose to touch on are the risks to the consumer from the residues of toxic substances which may remain in food that reaches the table, and the new risks to which domestic and farm, as well as wild animals and birds, and the flora of the countryside, are exposed as a result of the increasing use of toxic substances in farming practice.

Hazards to the Consumer

Let me deal first with the possible hazards that the consumer runs when he eats food which, at an earlier stage in its history, may have been treated with, or been exposed to, some toxic chemical. This was the subject of the Second Report of my Working Party. The first point which I wish to make is that when this report was published it was possible to write that " in spite of searching enquiries to as many official and unofficial bodies as one might suppose could provide relevant information, we have been unable to discover any specific instances of illness which have resulted from eating such food. The position does not, therefore, appear to have been established as one of immediate danger . . . ", even though it was " not one which allows of complacency."

It is only 4 years since this Report appeared. Yet so rapidly does the situation change that a year ago Davies and Lewis (1956) were able to show, with all the suspense of a detective story, just how real the dangers, in fact, are. The incident they described occurred in the county of Glamorgan, in a rural district with a population of just over 30,000.

One day the local Public Health Department was informed by telephone that 10 men at a local works had suddenly been taken violently ill. From the different circumstances in which they worked, it was apparent that the cause could not be something like gas or fume escape. Food poisoning being suspected, enquiries were made at their homes, and it was discovered that the only experience common to all 10 men was that they had eaten bread rolls bought at the same bakery. The baker was questioned, and it turned out that on the day in question he had returned 2 sacks of National Flour because of an odour which he could not identify. Later in the day, other people were reported ill, and a warning was consequently given over the radio that white bread rolls which might have originated from the bakery in question should be destroyed. By next day 47 people had been reported sick; and 12 hens to which the condemned rolls had been fed died instantly.

The 2 sacks of flour that had been returned by the baker were traced to a depot in Swansea, and then to the time, a few days earlier, when they had been loaded on to a rail wagon at Cardiff. Its number being known, the wagon was finally tracked down some 3 weeks later in Cambridge. Samples of the actual bread, scrapings from the wooden floor of the bakery storeroom, samples of the sacking, and scrapings from the floor of the van, were submitted to chemical analysis, and it was discovered that they were all contaminated with a substance called endrin. Endrin is used as a horticultural spray against various pests.

Further enquiry revealed that only one firm was importing endrin at the time, and that the same wagon which late in April had carried sacks of flour from Cardiff to Swansea had 2 months earlier been used to convey a load of the new pesticide. The endrin was dissolved in xylene for normal spraying purposes, and some of the containers had spilled. The story was now complete. What it proved was that a little endrin that had soaked into the wooden floor of a rail van was still able, 2 months later, to contaminate sacked flour sufficiently to bring about acute poisoning in men and animals.

I have begun with this arresting story, not only to indicate the enormous toxicity of the materials which are now in regular use in agriculture, but also to indicate the speed with which the world of toxic agricultural chemicals changes. Neither the report of my Working Party that was published in 1953, nor the later one which appeared in 1955, mentions endrin in a comprehensive catalogue of crop-protecting chemicals. Dieldrin and aldrin, two structurally-related compounds which also have their origin in dicyclopentadiene, are listed—but not endrin. Endrin, an isomer of dieldrin, is a new poison on the horizon.

The incident I have just described can justifiably be regarded as an isolated and accidental case which does not affect the generalisation we made in 1953, and to which I have already referred—even though food may, true enough, be contaminated in other ways during the course of processing for the market. What we are mainly concerned with here, however, is the possibility that food may contain the residues of chemicals which were applied either when the raw material was grown, or when it was stored, or which may have been picked up from packaging materials containing protective substances.

The list of toxic chemicals that are used in agriculture and on stored food is a very long one. Various insecticides, weed-killers, and fungicides are applied to crops in the field and to fruit and vegetables. Stored potatoes are treated with " sprout-depressants." Other stored foods, such as grain, are fumigated or sprayed or dusted with insecticides. And the rats which infest food stores are attacked with bacterial and chemical preparations—which may by accident then contaminate the food.

Chemical Protection of Growing Crops

Until the Second World War, the toxic substances which were used to protect growing crops were mainly chemical compounds containing lead, arsenic, or copper. Working limits for residues in harvested crops and fruit have been agreed for arsenic and lead, and in the case of a few specified foods, for copper, and none of these substances provides any major problem to the chemical analyst. Controlling their use is therefore essentially an administrative problem. It is the substances which were introduced during and after the Second World War that create the real difficulty. They include a variety of halogenated compounds, of which the better-known are DDT,

BHC, dieldrin, carbon-tetrachloride, methyl-bromide, and now endrin; and a series of organophosphorus compounds, among the best-known of which are parathion, TEPP, Schradan, and Metasystox. There are also nitrophenol compounds such as DNC, and various compounds of vegetable origin, such as nicotine and derris. In addition—as already indicated—we need to remember that stored food may become dangerously contaminated by various chemical and bacterial rodenticides.

Provided they are not improperly used, some crop-protecting substances have chemical or physical properties which give all the necessary assurance that they could not be present as residues on harvested crops. Among these are such highly dangerous substances as TEPP and nicotine. Other chemically stable substances are more persistent physically, and residues may remain on harvested crops or stored food until they are ready to be consumed. Some may then disappear during cooking, but a few are not so easily disposed of.

So far as our home-grown staple foods are concerned, my Committee, after reviewing all the available evidence, concluded that there is little danger to the public arising from the use of such crop-protecting chemicals as the fungicides that are used to dress wheat seed, or the selective weed-killers with which wheat is customarily sprayed well before it is due to be harvested. On the other hand, it is fairly certain that DDT, which is used in dairy farming, may lead to the presence of abnormally high amounts of DDT in milk and body fat—as has occurred in the U.S.A.

The position is more dangerous in the case of such seasonal fruit and vegetable crops as strawberries, brussels sprouts, and hops. These are the crops to which the systemic and contact organophosphorus insecticides like metasystox are normally applied. Such chemical preparations constitute a hazard since they may be left as residues in food. Fortunately, we are beginning to learn something about their toxicity in man and animals. Some, such as methyl bromide, which is applied to stored wheat, may also destroy an essential factor in the food. There have been cases in which such systemic pesticides have been used carelessly and in which treatment has been applied at too short an interval before harvesting. There have also been cases in which stored food has been contaminated by chemical and bacterial rodenticides.

It is difficult enough to control the hazards where home-grown food is concerned. But the greater difficulty derives not from that proportion of our food which we produce ourselves, but from the 60 per cent. or so which is brought in from abroad, and whose previous history is inadequately known—or not known at all.

Three Necessary Measures

Three things are needed, according to the second report of my Working Party, if measures designed to control the use of toxic substances in agriculture are to be effective from the point of view of the consumer. They are:—

(i) A knowledge of the nature and extent of the use of all toxic substances in agriculture and in food storage.

(ii) Methods of analysis which allow the extent of any food contamination to be determined.

(iii) Adequate information about the toxic properties of the materials as they affect mammals, so as to allow a reasonable assessment to be made of the human risk.

These desiderata would, of course, be adequately met if the following conditions could be generally applied:—

(i) A firm proposing to sell a new chemical which, if used for its advertised purposes, might contaminate food, should be responsible for providing adequate information about methods of analysis and toxicity before offering the material for sale. This, in effect, is what the Pure Food and Drugs Administration of the U.S.A. demands.

(ii) The Government Departments concerned should satisfy themselves that the public would be adequately protected from any potential risk that might arise from the use of the proposed new material.

Happily, because of the co-operation of industry, we are beginning to satisfy these requirements. But, as was pointed out in the Second Report of my Working Party, the position is still that:—

(i) Many of the firms producing these materials do not have adequate facilities for obtaining the necessary toxicological data about the materials they produce. Nor are there yet available co-operative research laboratories which they can pay to do this work for them.

(ii) There would be nothing to stop firms which refuse to co-operate from marketing compounds for use on food crops without any reference to official bodies.

(iii) Government Departments must depend on the goodwill of the firm concerned for obtaining adequate information about the introduction of new preparations. This they have received in full measure. But nevertheless officials cannot be expected to have a complete knowledge of new compounds and the extent to which they are used.

(iv) Precise information about the way a given shipment of imported food has been treated before purchase is often unavailable. Even if the practical as opposed to theoretical facilities were available to permit the formidable task of undertaking analyses of all imported food cargoes, it would not be possible to obtain a complete check owing to the difficulties in sampling and, in some cases, to the absence of chemical methods of detection.

We are thus faced by an extremely difficult problem. The elimination of agricultural waste has become the declared and useful object of a powerful branch of the chemical industry, and each year sees an increase in the number of pest- and weed-killers, whose collateral toxic effects are in general insufficiently known. It would be as unreasonable to stem this technological development because of the possible, but undefined, hazards it entails as it would be to deny the existence of a problem and the need for

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measures by which it could be minimised. But the fact remains that public fears about the dangers of chronic illness from eating food that might possibly be contaminated are hardly going to be allayed by statements that there have been few, if any, fatal accidents from this cause, or that chronic illness is not to be expected because none was observed in experimental rats which over a year or so ate food that had been dosed with the new chemicals used in crop protection. Disquiet will give way to confidence only if the public is satisfied that a constant watch is being kept over the problem, and that every reasonable precaution is being taken to obviate possible risks.

This was the view of my Working Party. But because of the technical difficulties involved, we did not advocate any new legislation in order to bring the use of crop-protecting materials under closer supervision. Instead, we advised that the appropriate Departments should set up a Working Advisory Committee to consider the risks to the consumer, and to guide Departments as to the scope of the initial investigations which should be undertaken by manufacturers, and about the evidence which should accompany proposals to introduce new substances. It was also suggested that this Committee should assume the responsibility for advising Government Committees, where necessary, about the maximum permissible limits for residues arising from the use of toxic substances on agricultural products and in the storage of food. And we also advised that statutory powers should be sought only if the industries concerned proved reluctant to co-operate with Departments about the introduction of new toxic substances. I am happy to say that so far industry and officials have worked together in confidence and successfully. There is every indication that they will continue to do so.

Toxic Dangers to Animals

Let me now turn from the human consumer to the dangers which the new pesticides and herbicides bring to domesticated and wild animals, as well as to the flora of the countryside. As the third report of my Working Party pointed out, the public is concerned about these matters because of at least three distinct considerations. The first is the quite straightforward fear that the accidental destruction of wild animals and plants may affect the balance of life throughout the countryside. The second is that most normal people do not like seeing the corpses of animals which have been accidentally killed by toxic sprays, and are disturbed when they think that these treatments may have caused suffering and pain. The third is the unsightliness, however temporary, of verges or hedgerows that have been accidentally, or deliberately, sprayed.

In approaching the problem, we were thoroughly aware that there is no such thing as a balance of nature that is fixed in time. The balance changes with every step in the evolution of plants and animals. The trouble, however, is that modern man is probably a more rapidly-acting and more far-reaching factor in this process of evolution than any that have gone before. We have destroyed forests and exterminated animal species, and this process has intensified progressively over the past 4 centuries. The essential question we have had to ask ourselves is whether the chemicals now being used in farming constitute a more serious hazard to the fauna and flora of our land than did earlier innovations in farming and forestry practice. We have to ask this question knowing full well that as the world's population increases in size, the intensity and extent of agriculture will also have to increase. We need to assure ourselves, therefore, that our new chemical pesticides do more good than harm, not only immediately, but also in the long term, before we accord them a general blessing. And we have to do this knowing that in the end only time can provide the real answer.

Many toxic chemicals such as nicotine, derris, and compounds of copper have been in use for many years, and we know enough about them to prevent them becoming a menace to the wild life of the country. On the other hand, arsenic, in the form of arsenates and arsenites, which had also been used for a very long time, is still a source of danger, especially to bees and, in a new use, to farm animals which gain access to sprayed potato crops. As before, however, the main danger lies with such newer pesticides as the organophosphorus compounds. The aim of the research workers who devise these substances is, of course, that they should be toxic only to specific pests. But as we all recognise, this aim is not going to be easily, if ever, achieved—for the good reason that many of the chemical processes which govern the living matter of plants and animals are the same. A chemical which will kill one kind of animal is, therefore, likely to kill another. In the circumstances, it is not at all surprising that in spite of all the laboratory tests and field trials which may precede the release of a new chemical for general use, unforeseen and undesirable collateral effects may come to light only during a period of full-scale introduction, or after several seasons' use. And as my Committee was careful to point out, over and above this we shall always find it immensely difficult to decide whether any collateral effects are really deleterious from the point of view of the balance of nature, since their possible effects have to be disentangled from those due to a variety of other factors which also influence the natural cycles of animal and plant populations—and which we need to remember influenced these cycles long before there ever was a chemical industry.

The factors which in theory govern the incidence and extent of casualties among wild birds and mammals are best classified, so my Committee felt, in the following way (1955):—

1. *Chemical used and its method of application*
   (i) The toxicity of the main active ingredient of the pesticide to different species; including that caused by inhalation, by external contamination of food or drink, or by a combination of these factors.
   (ii) The influence of manufacturing impurities, wetting agents, solvents, diluents, activators, and other ancillary chemicals.

(iii) The method of application, *e.g.* high or low volume spraying, " mist blowing," dusting, or soil treatment.

(iv) The concentration at which the chemical is applied.

(v) The persistence of the chemical after spraying, *i.e.* its chemical or physical stability after spraying, and its solubility in rain or its rate of absorption into the plant tissues.

(vi) The possibility that vegetation that has been sprayed may be more (or less) attractive to the mammal or bird than untreated vegetation.

2. *The species of animal and its habits*

(i) The numbers and species of mammals and birds frequenting the sprayed area, and their respective sensitivities to the chemical used.

(ii) The feeding and drinking habits of the different species.

(iii) The age, body-weight, and food consumption of the species.

(iv) Movements of the species during and soon after spraying.

3. *The environment*

(i) Type and abundance of pests in the treated area, and their consequent influence on other animal life.

(ii) Features in area or crop favourable to animal life, *e.g.* for nesting, shelter, safety from predators, warmth, regular food and water supplies.

4. *The climate and season*

(i) Season of the year, with its influence on alternative food and shelter crops, migration, hibernation, harvesting, hedge berries, farming activities.

(ii) Weather conditions during spraying, which affect chemical persistence.

(iii) Occurrence of drought, with resultant tendency of creatures to drink spray on vegetation or heavy dews on recently sprayed vegetation.

Such new evidence as has emerged since the appearance of our report two years ago does not suggest that there is any need to qualify these generalisations. But it is necessary to add one. Through the ordinary process of natural selection, " insecticide resistance " is believed to be developing fast among insect species of economic importance. According to a recent statement, the number is already near a hundred, and tolerance is now reported not only to DDT and its related compounds, but also to such chlorinated hydrocarbons as BHC, dieldrin, aldrin, and even endrin; and, in a smaller number of cases, to the organophosphorus insecticides (Ripper, 1957). This means that until new methods of control become available, there will be a tendency for farmers to use larger quantities of toxic chemicals in their efforts to control the pests they are always fighting. In turn, this may well mean an intensification of the dangers of collateral effects—at any rate, for an intermediate period—with, in the case of non-harmful species, a chance of natural selection bringing about unpredictable changes in insects that at present may not only be non-harmful, but even beneficial.

So far as farm animals are concerned, the actual risks have been recently outlined by McGirr (1956), in a paper presented to the 74th Annual Congress of the British Veterinary Association. As he points out, fatalities resulting from the consumption of lead-contaminated materials are still among the most common causes of poisoning on the farm. Here the risk comes from animals licking painted wood or metal, and a host of other materials which incorporate lead in one form or another. Arsenical poisoning is also of frequent occurrence, and as already observed, is usually due to stock gaining access to sprayed crops through open gates or broken fences, or to spray drift. Another cause of danger is carelessness in disposing of arsenical sheep and cattle dips. Copper compounds also claim their victims, particularly in sheep. Here again, the danger usually occurs when sheep stray into orchards that have been sprayed with copper-containing fungicides. Acute fluorine poisoning also occurs occasionally. One of the more scientifically interesting stories which McGirr reported relates to bovine hyperkeratosis, or X-disease, which after considerable research, was shown to be due to the ingestion of highly-chlorinated naphthalines that are used as lubricants in food-pelleting machines, or as grease on farm machinery. Among the other points emphasised by McGirr were the dangers of rodenticides, and the ways in which organomercurial fungicides, the chlorinated hydrocarbon and organophosphorus insecticides, as well as the dinitrophenol group of insecticides and herbicides, to which I have already referred, add to the hazards of the farm animal's life. I shall not attempt, therefore, to embellish the picture he painted.

But one point must be emphasised. By and large, the responsibility for the accidental poisoning of farm animals must mainly rest with the farmer and farm worker. If the reasons why it is necessary to advise extreme caution in the use of toxic chemicals were fully appreciated, and if clear instructions were followed, there would be many fewer cases of poisoning of farm animals than actually occur. Of course, a contributory cause of these accidents may well be, as my Committee suggested, " the natural curiosity of animals which simply for that reason wander into a field where spraying is taking place or has just taken place." But this can be only a contributory cause.

It is difficult to take quite the same view about responsibility where the poisoning of bees is concerned. Bees, as insects, are a natural target for many of the toxic sprays used in agriculture. Until recently, arsenical sprays were the only lethal substance which really mattered here. Since the new crop-protecting chemicals were introduced, losses from chemical poisoning are claimed to be at least twice what they were formerly. According to the evidence which was brought before my Committee, accidents occur most consistently and most seriously in areas where brassica seed crops are grown extensively.

What the position is to-day I am not quite sure, but two years ago it was still possible to write that arsenical insecticides remained the most serious hazard against which the bee-keeper had to guard. Among weed killers, concentrated sprays containing DNC were then responsible for most damage to bees. Hormone weed-killers also had an important damaging effect by seriously reducing the succession of weed flowers which provide nectar and pollen.

Among the chlorinated hydrocarbon insecticides, BHC is certainly the most dangerous. Chlordane and DDT are also toxic, although the latter has not been proved in practice to be the menace it was expected to be when first introduced. Toxaphene, a member of the same group of chemicals, is reported to be safer than either BHC or DDT.

Among the organophosphorus insecticides, parathion is the most dangerous to bees; particularly when, even if rarely, it is used as a spray. The systemic insecticide schradan is much less dangerous, but more widely used.

The Ministry of Agriculture is thoroughly aware of the dangers, and each year issues a press notice appealing to fruit growers to exercise care in the application of orchard sprays in view of the hazards which this practice brings to bee-keepers. It would be interesting to find out whether the general publicity which is accorded the problem, not only in this way, but also in the farming, horticultural, and bee-keeping press, as well as through the B.B.C., would have a greater effect if it were reinforced by local articles and appeals, as was suggested by my Committee.

One interesting general point emphasised by my Committee was that insect populations may be affected either directly by the use of chemicals designed primarily to destroy pests, but incidentally also killing natural predators and parasites, as well as useful pollinating insects, of which there are many besides the domesticated honey bees; or indirectly by the use of herbicides. The second is widely regarded as a more important factor in the long run.

The danger of disturbing the balance between pest insects and their predators and parasites has long been recognised, but far too little attention has yet been given to the problem as a whole, in spite of its economic importance to cultivators.

Another difficulty to-day, to which I have already referred, is the appearance and spread of strains of insect which are resistant to the insecticides being used. This possibility has been realised for some time, but it became prominent only with the discovery of DDT-resistant flies.

I shall not consider the problem of the contamination of rivers and ponds in which fish live, since crop-protecting chemicals cannot possibly affect them in the ordinary way, and since legislation exists in order to prevent streams or ponds being polluted by washing out drums which have contained concentrated chemicals.

Wild Animals and Birds

Wild animals and birds are in a completely different category. For some years now deaths have occasionally been reported amongst game, vermin, and other wild life, after fields and orchards have been sprayed with various forms of toxic chemicals. On the other hand, when my Committee reported on this matter in 1955, it found that the total number of such casualties in the average spraying season was not only small, but trivial when compared with other causes of death. However, in the isolated instances in which casualties had occurred, all manner of creatures had been affected, from birds to foxes and rats. Our view was that the most dangerous treatments, in order of importance, were: organophosphorus insecticides applied to brassicas in late summer; and arsenicals applied for potato haulm destruction in September. Casualties had also occurred occasionally with dinitro weed-killers applied to corn and peas between March and July; and with DDT insecticides used on carrots and peas. While this summarised the evidence for the period which we investigated, we realised that the same pattern would not necessarily apply to every spraying season, as a variety of factors affect the way casualties occur.

Because the evidence was so scanty, we carried out 2 experiments on 3 fields of winter wheat in Norfolk that had been sprayed with DNC weed-killer, and on 3 fields of brussels sprouts in Worcestershire that had been treated with Schradan insecticide. Counts of the wild population were made before the application of the chemicals, and the fields were combed for the bodies of dead creatures after spraying had been completed. The results were either reassuring or disappointing, depending on the way one viewed the problem. The decrease in numbers of birds and small mammals did not exceed what would have been expected on the basis of normal fluctuations. In short, this particular experiment confirmed the general view that agricultural spraying hardly adds to the hazards run by the wild life of this country.

Since then, many new reports have been received about unusually heavy deaths occurring amongst wild and game birds, and an investigation of the circumstances of a number of these incidents that occurred in the spring of 1956 suggested that a seed dressing, probably a dieldrin dressing, was responsible. *Post-mortem* examination in a number of instances was unable to establish the circumstances with any certainty, and in consequence, an experiment was carried out in which dressed grain was fed to domestic pigeons and pheasants at the Veterinary Research Laboratory. A report of this work has now been published by Carnaghan and Blaxland (1957). Its results are sufficiently striking to suggest that the widespread use of seed dressings containing dieldrin may have been responsible for the mortality which occurred in wild and game birds in the spring of 1956. Unfortunately, there has been a recurrence of these incidents in 1957, and the problem is now receiving renewed attention from a special sub-committee of the Inter-departmental Advisory Committee.

Before I conclude with one or two general observations, I wish to put on record the fact that my Committee was also very concerned, as is the Inter-departmental Advisory Committee which is now charged to consider these problems, about dangers to the wild flora of our countryside, resulting from

the increasing use of selective weed-killers. Here, however, we were faced by an even greater ignorance of what the significant issues were. Hedges, borders of fields, and roadside verges are semi-natural communities whose characteristics have been determined very largely by human intervention. Changes in the composition of such floral communities will obviously lead to a new ecological situation. But will they necessarily be worse from the biological point of view than those man has already caused? We had to conclude, therefore, that the net result of spraying might be to produce roadside and hedgerow communities which were different from the old, but which still contained species that were undesirable both from the point of view of the agriculturalist, and of the road engineer. At the same time, spraying might remove many harmless and even beneficial species, such as those which contribute to the food chain of insects and birds useful to agriculture. The situation is one which can be properly described in the sober terms—" it wants watching."

Conclusion

And this is what needs to be said about the whole field in which the new chemicals used in agriculture may exercise their collateral hazards. In essence, the general problem I have been discussing is, therefore, little different, except in scale, from the question of the radiation dangers which has taken such a grip on the public imagination. Both constitute potential hazards whose scale cannot be properly estimated for lack of the necessary information. But this information, we can be sure, will undoubtedly be forthcoming. In the case of agriculture, with Governments so alive to the hazards, and with industry becoming more and more aware of, and more willing to discharge, the responsibilities that are entailed in introducing new practices into an old calling, the public can rest assured that what can be done to reduce the collateral hazards of new agricultural techniques will be done. As I have already implied, the hopes that lay behind the establishment of the official Advisory Committees on Poisonous Substances in Agriculture have been fully realised in the co-operation this Committee has received from manufacturers, who are becoming more and more alive to the need for more analytical and toxicological work before putting new products onto the market. Questions such as those which relate to the detection of chemical residues in food; to the reduction of spray drift; and to the appearance of insecticide-tolerant strains, are thus receiving increasing attention, and will no doubt find their answers. We may still see established a Co-operative Biological Testing Station to help define, and so reduce, the collateral hazards of crop treatments. But however long it takes before such a Station does materialise, we may feel certain that those who have a vested interest in developing new techniques in agriculture also have a vested interest in seeing that these techniques produce more good than harm. This is true not only of manufacturers in Great Britain, but also of those in other countries which are as advanced socially and industrially as our own.

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The Chairman, Mr. E. R. Callender, introducing the author, said that in addition to being Professor of Anatomy at Birmingham University, Sir Solly was a member of the Agricultural Research Council and secretary of the London Zoological Society. The subject was one of great importance to all as the spraying of crops was now an essential part of good husbandry. In view of the toxic nature of many of the products used, however, spraying was not without its hazards to the human and the animal population. The interest in the Session was well evidenced by the attendance. The address followed.

Thanking the speaker, the Chairman said they were indeed fortunate that, despite a very busy life, a scientist of the calibre of Sir Solly had found time to attend and to give such a masterly survey of the subject. He had brought to them all a wealth of information on a topic of very great importance, and on behalf of all he extended his deep gratitude to the speaker. (Loud applause.)

Research Problems in Animals Reproduction

BY

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THE perfection of artificial insemination as a means of animal breeding has been largely responsible for providing one of the most powerful and fruitful stimuli to modern scientific investigations on reproductive processes, particularly in large domestic animals. At the same time, however, advances in A.I., probably because of their great practical value, have often tended to overshadow the importance of certain other equally original though less spectacular, developments in the science and practice of animal reproduction. It may be fitting, therefore, on this occasion, when addressing an audience well acquainted with the problem of artificial insemination, to concentrate chiefly on those other, probably less known studies in reproductive physiology, in which progress has been particularly rapid and which continue to advance with exceptional speed and vigour.

It would be quite impracticable to attempt to enumerate here, however briefly, all the recent advances in research on animal reproduction. Having just completed, in collaboration with my wife, a chapter on "Reproduction" for next year's "Annual Review of Physiology," I am only too well aware what an impossible task that would be. In this chapter, in which we tried to review published work on reproduction covering the period of the past twelve months, we have had to abstract no fewer than 468 publications, an output equivalent to that of one to two scientific papers published each day of the year!

Before turning to some of the more specific issues which confront research workers engaged in studies on reproduction, I should like to deal briefly with a more general problem of sex physiology on which a great deal of attention is focused at present, namely, the problem of:—

Sex Ratio, Reversal and Determination

In his famous book on "The mechanism and physiology of sex determinations" Richard Goldschmidt (1923) used these words as the opening sentences to the chapter on "The numerical ratio of the sexes":—

"There is scarcely any branch of biology in which so much nonsense has been talked as in the discussion on the connexion of the numerical relations of the sexes to the problem of sex determination. The older investigators, who did not know of the mechanism of sex distribution, can be excused when they confused a shifting of the sex ratio with a sex determination. To-day, however, there is no room for excuse, as has been pointed out already by different authors. Where a shifting of the ratios of the sexes is experimentally successful, it can be due to many causes arising out of the mechanism of sex distribution; but only in the rarest cases is there a real sex determination, that is, either a directional influence on the distribution mechanism or an influencing of the physiology of sex determination."

By and large, the present situation is not very different from what it was nearly forty years ago, when Goldschmidt wrote these sentences, though, admittedly, much progress has been made since that time in the elucidation of the various factors which can influence the ratio between the two sexes in man and animals alike.

It is as well to remember that the Wolffian, or mesonephric ducts, from which the male sexual structures develop, exist during the early stages of foetal life in both sexes. In the female rabbit foetus, for example, these ducts persist normally until the twenty-fourth day of foetal life, and regress only during the last week of pregnancy. In the male foetus they do not regress but develop into *vasa deferentia* and *vesicae seminales*. However, they regress in males also, if castration of the foetus is performed before the twenty-second day of pregnancy. The urogenital sinus provides another interesting example. This part also is identical in young male and female rabbit embryos, and during a limited period of time it is possible to "masculinise" the female urogenital system by testosterone, just as it is possible to prevent the normal development of the masculine sinus and the appearance of prostatic buds by castrating the male early in its foetal life, namely on the nineteenth day of pregnancy. Results of studies on the pituitary gland in the foetal rabbit strongly suggest that it is actually this organ which controls the normal development of the foetal sexual structures (Jost, 1953, 1956).

A rare example of a spontaneous hormone-dependent sex reversal from male to female in adult domestic birds, has been recently described in a Brown Leghorn capon, and the cause was traced to the growth of a Sertoli cell tumour endowed with oestrogenic activity sufficiently powerful to induce a change from male to female plumage (Siller, 1956).

It is conceivable, in view of the difference in sex-determining chromatin between the "female-determining spermatozoa (which carry the X-chromosome) and the "male-determining" spermatozoa (which carry the Y-chromosome) that the sex ratio could be influenced experimentally if means could be found for segregating the two kinds of spermatozoa and then utilising only the one or the other kind for fertilisation. During the last year alone, there have been, in fact, at least two attempts at modifying experimentally the sex ratio in animals: the first was made at Uppsala by Lindahl (1956), who subjected bull semen to centrifugation in his counter-streaming centrifuge and obtained two sperm fractions, one

"heavier," *i.e.*, of higher, and the other "lighter," *i.e.*, of lower, specific gravity. When the heavier sperm fraction was used to inseminate 24 cows, 12 became pregnant, giving birth to 11 live calves, all of them male. Lindahl is now conducting in Sweden a similar but much larger field trial, involving several hundred head of cattle; the outcome of this trial will be eagerly awaited. The other attempt comes from McWhirter (1956) at Oxford, whose theory is based chiefly on some earlier experiments on mice by Weir (1949, 1955). He claims that by selecting animals for high and low *p*H values of blood, it is possible to show that males belonging to the "acid" line are predisposed towards producing an excess of daughters, while males of the "alkaline" line are predisposed to an excess of male progeny. Again, much more experimental evidence is required in support of this concept.

Much firmer evidence is available at present in support of another idea, namely that sex can be diagnosed early in foetal life as well as after the death of the animal, by histological examination of cell nuclei in somatic tissues. This idea has been gaining ground rapidly since 1949, when Barr and Bertram first described a definite sex difference in the structure of intermitotic nuclei in the nerve cells of the cat, pointing out that in female cats, but not in the males, there is a fairly conspicuous mass of chromatin, a so-called nucleolar satellite, which lies in most instances closely against the inner surface of the nuclear membrane. Similar observations were soon made on various somatic cells of other mammalian species including man, and are being utilised successfully for clinical and forensic purposes of sex diagnosis. Such evidence as is available indicates that the sex chromatin of female somatic cells represents a fusion of heteropycnotic portions of the two large X-chromosomes, while in the male the complex of one X-chromosome with the small Y-chromosome fails to form a chromatin mass of comparable size (Moore & Barr, 1954). During the last few years several methods for accurate sex determination have been developed from blood films in man (Riis, 1957; Peiper & Oehme, 1956; Kosenow, 1957; Tenczar and Streitmatter, 1956; Ashley, 1957), dog (Porter, 1957) and rabbit (Luers, 1956) and from the epidermis of cat (Graham & Barr, 1952) and man (Moore, Graham & Barr, 1953; Dixon & Torr, 1956). The morphological sex difference in the chromatin of skin in particular was shown to persist for a considerable time after death. In pregnant women, correct prenatal sex diagnosis has now been attempted by "cellular sexing" of the placental endothelium and of cells obtained by direct aspiration of amniotic fluid (Bohle & Hienz, 1956; Sachs, Serr & Danon, 1956; Makowski, Prem and Kaiser, 1956; Glenister, 1956). In rats, ameloblasts from the dental germ of one-day-old animals have been used for the purpose of sex differentiation (Castro, Silva Sasso and Goes, 1956).

Before leaving the subject of sex ratio, reversal and diagnosis, I may perhaps be permitted to make a brief reference to another, possibly related, problem, namely that of changing breed characteristics between animals belonging to the same species. In April, 1957, Benoit, Leroy, Vendrely and Vendrely reported to the French Academy of Sciences that by injecting into the White Pekin duck deoxyribonucleic acid prepared from testis and blood corpuscles of the Khaki Campbell duck, they succeeded in changing certain breed characteristics of the Pekin duck into those of the Khaki Campbell. The changes which they observed as a result of intraperitoneal injections of "DNA" included increased deposition of pigment in the beak and plumage of the White Pekin duck, and some rather remarkable modifications in the shape and general appearance of the duck's head and whole body. Should future investigations confirm the view held by the French authors, that the changes which they observed are, in fact, dependent on "somatic mutations," then this would indicate that such mutations, hitherto known to occur in micro-organisms, can also take place in higher animals.

The next problem in reproductive physiology on which I should like to touch briefly concerns:—

The Rôle of Hormones in Reproduction

Again, instead of a comprehensive review of all the manifold aspects of this complex and rapidly expanding field, I propose to deal only with a few examples, mainly derived from some recent investigations on the mode of action of oestrogens, progestogens, androgens and gonadotrophins.

Oestrogens and progestogens

Among the recent developments relating to the function of oestrogens and progestogens, those concerning the metabolic effects and metabolic pathways are particularly impressive.

One of the best known metabolic actions of oestrogens which has found application in the practice of animal breeding is the fattening of domestic birds by implantation of diethylstilboestrol. This oestrogenic effect has been shown to depend on a number of processes induced by stilboestrol in the lipid metabolism, including stimulation of lipogenesis in the liver, increase in the lipid level of blood, and lipid deposition in the tissues; these changes are known to be associated with, or followed by, profound alterations in the calcium and phosphorus metabolism of the animal body (Lorenz, 1954). A closely related metabolic effect of oestrogens which has also been suggested for use in animal production is the growth-promoting and fattening action of stilboestrol in sheep (Andrews *et al.*, 1949; Jordan, 1950; Hale *et al.*, 1955; Jordan & Croom, 1956), cattle (Dinusson *et al.*, 1950; Burroughs *et al.*, 1954; Klosterman *et al.*, 1955; Andrews *et al.*, 1956; Kastelic *et al.*, 1956) and pigs (Braude, 1947, 1950). Two other peculiar effects of oestrogens which deserve to be mentioned here since both were found to be of great practical significance, are the suppressing action of ovarian oestrogens on microbial infections of the bovine uterus (Rowson, Lamming & Fry, 1953) and the action of genistein, an oestrogen present in the subterranean clover, *Trifolium subterraneum*, and possibly also in other pasture plants, which is responsible for several

reproductive disorders in sheep (Bradbury & White, 1951; Curnow, 1954; Pieterse & Andrews, 1956).

Research concerning the metabolic pathways of the oestrogens in the animal body has been reviewed on several occasions during the last few years, notably also by Samuels (1955). It is one of the most striking recent findings that oestrogens, progesterone and even testosterone are to a certain extent "interconvertible" owing to the presence of specific enzyme systems in animal tissues. Another equally important fact which emerged is that within the same functional group of hormones such as, for example, the various oestrogens, these too are subject to reversible enzymic transformations. Thus, oestrogens are now believed to be mutually interconvertible according to the general scheme:—

$$17\beta\text{-oestradiol} \rightleftharpoons \text{oestrone} \rightarrow \text{oestriol-3, } 16\beta, 17\beta$$
$$\Updownarrow$$
$$17\alpha\text{-oestradiol}$$

In the living animal, the liver plays a major rôle in the inactivation of oestrogens, but other tissues, including the uterus, also appear to participate in the process of metabolic inactivation.

Progestogens, like oestrogens, seem also to be metabolised chiefly in the liver, but the metabolic pathways are by no means clearly understood. One has only to recall that pregnane-3, 20-diol, which is generally regarded as the most abundant urinary metabolite of progesterone accounts merely for a small fraction of the progesterone which undergoes metabolic breakdown in the living body. When progesterone is injected into men or non-pregnant women, not more than 15 per cent. appears as pregnanediol in the urine; in pregnancy, however, a recovery of 30 to 35 per cent. has been reported. The greater portion of injected progesterone still remains to be accounted for, and future investigations will probably reveal the existence of several as yet unknown progesterone metabolites. This is indicated, among others, by some recent work on the human placenta, which showed that this organ contains in addition to progesterone no less than 7 other steroids with ultra-violet absorption maxima at 240 mμ (Jones, Berliner & Salhanick, 1955). During a recent study of progesterone in the domestic animals, Short (1956, 1957) obtained strong evidence for the existence of several progestogens in placental tissue; in mare placental extracts for instance, he identified 20β-hydroxypregn-4en-3one, a progesterone metabolite closely related to 20α-hydroxypregn-4en-3one which occurs normally in the human placenta. In connexion with Short's studies it is also worth noting that in the domestic animals progesterone occurs not only in the ovary and placenta but in the peripheral blood as well. Chromatographic analyses, however, show that the peripheral blood level of progesterone in pregnant cattle, sheep and pigs is very much below that previously recorded in the blood of pregnant women.

A notable achievement in research on progesterone is the successful chemical synthesis of a whole range of compounds endowed with progestational activity (Ferin, 1956; Overbeek & Visser, 1956; Reifenstein, 1957; Engel & Noble, 1956; Pincus, Chang, Zarrow, Hafex & Merrill, 1956). Some of these new synthetic compounds were shown to be so effective in inhibiting ovulation that they have been classified as "anti-fertility factors," and are even considered by some investigators for use in controlling fertility (Pincus, 1956; Pincus, Chang, Hafez, Zarrow & Merrill, 1956). Certain other of the new progesterone derivatives possess marked anti-luteinising activity and act probably by competing with progesterone, that is, in the same way as some enzymic inhibitors, by competing with natural substrates for certain enzymes (Mardones, Iglesias & Lipschutz, 1956).

Another useful addition to research on progestogens has been the elaboration of a new, simple and rapid enzyme test for assaying the potency of progesterone and related steroids (Lutwak-Mann & Adams, 1957). This test is based on the observation that the progestational response of the rabbit uterus to progesterone and related compounds is closely correlated with the activity of carbonic anhydrase, an enzyme which is present in the rabbit endometrium. Unlike the previously used histological bio-assay method, which depends on measuring the degree of proliferation in the endometrium, the enzymic test of luteoid activity is not only incomparably more rapid and simple, but it is moreover objective and quantitative.

Androgens

As with progesterone, much of the basic information from which our knowledge of androgen activity originated was derived from anatomical and histological studies. These same studies provided also largely the inspiration for the so-called biological assay methods whereby one could detect and determine the action of male sex hormones.

The chief method available in the past for assessing the effect of male sex hormone on accessory organs depended on a morphological analysis of these organs, such as the prostate or seminal vesicle. However, an examination of this kind can only be performed after the animal has been sacrificed, the abdomen opened and the glands dissected for anatomical and histological examination. This approach, not really applicable to either man or to large domestic animals, was mainly confined to small laboratory animals. In recent years, however, this difficulty has been overcome, at least partly, by applying certain methods of semen analysis to the problem of assessing the male sex hormone activity in the living animal (Mann & Lutwak-Mann, 1951; Mann, 1954*a*, 1956). The facts on which such androgen assays are based are discussed in the following:—

The last few years have witnessed the identification in the secretions of male accessory organs of a number of specific chemical constituents such as fructose, inositol, ergothioneine, and glycerylphosphorylcholine. These substances are produced in the accessory organs under the influence of the male sex hormone. When an animal is castrated the secretory function of the accessory organs ceases forthwith and these substances are no longer produced. However, following the administration of testosterone the accessory organs of the castrated male promptly resume their secretory function, and all the characteristic substances

reappear in the secretions. The best illustration, perhaps, of this highly specialised chemical function of the male accessory glands, and of its strict dependence upon androgen is contained in experiments which make use of subcutaneous transplants (Lutwak-Mann, Mann & Price, 1949). When tiny fragments of the accessory glandular tissues form one male are transplanted into the abdominal subcutaneous sites of another, they continue their specific activity, namely, the secretion of fructose and citric acid, provided the host animal remains under the control of the male sex hormone. Even if the male accessory gland tissue is transferred into a female rat, it will grow subcutaneously and produce ample fructose and citric acid, if the female host is treated with testosterone.

Since the secretions of the male accessory organs form part of the seminal plasma, the secretory activity of such organs as the prostate or seminal vesicle can be evaluated by a chemical analysis of the seminal plasma, that is, of the acellular portion of semen. The obvious advantage which chemical methods of semen analyses possess over the older bio-assays is that one can study the functional state of the male accessory organs and thereby of androgenic potency in *live* animals, at frequent time intervals, and if necessary, over a period of months or years.

Our investigations on the development of reproductive function in the young rabbit (Mann & Parsons, 1950), rat (Mann, Lutwak-Mann & Price, 1948), bull (Mann, Davies & Humphrey, 1949) and boar (Mann, 1954b) have established the fact that in male animals, the onset of the secretory function of the male accessory organs precedes considerably the appearance of the spermatozoa. In bull calves for instance, already at four months we found appreciable quantities of both fructose and citric acid in the secretion of the seminal vesicles, whereas the first mature spermatozoa only appeared several months later. At the age of one year, the bull seminal vesicles are approaching maximal secretory activity as indicated by peak values for fructose and citric acid in semen, but the rate of sperm production is still on the increase. These observations, coupled with knowledge of the intimate dependence of the secretory processes in accessory organs upon the male sex hormone, lead us to conclude that the onset of male hormone activity precedes the appearance of spermatozoa in the animal body. One cannot, and must not, exclude the possibility that there may be functional androgens in the male even before the onset of secretory activity in the accessory organs; it is conceivable that in the bull calves, for instance, the testicular hormone may be active even before the animal is four months old, but if so, then either the level of androgen in the very young bull calf is exceedingly low, *i.e.*, too low to stimulate the formation of fructose and citric acid in the seminal vesicles, or else the action of androgen is opposed by some other factors.

A certain doubt exists as to what constitutes the "male sex hormone" and how much of the total androgenic activity in the male at any given stage is due to testosterone. However, the recent demonstration by chemical means that testosterone is present in the blood from the human spermatic vein but is absent from the arterial blood, indicates clearly that testosterone is not only produced in the testes but is, in fact, secreted by the male gonads (Lucas, Whitmore & West, 1957). As regards androsterone, a long-established main urinary product of testosterone metabolism, it too has now been isolated from the plasma of peripheral blood and thus shown to circulate in the male organism (Migeon, 1956).

Metabolic effects of testosterone on tissues other than the reproductive organs represent another fruitful line of modern research on androgens. A peculiar renotropic effect of testosterone has been described: the inhalation of small amounts of chloroform by mice induces extensive necrosis in the renal tubules of male, but not female, mice; female mice, however, can be made susceptible to renal necrosis by injections of testosterone, while male mice can be rendered less sensitive by castration (Culliford & Hewitt, 1957). When, however, increasing doses of androgen are administered to castrated mice, the amount of damage rises proportionally (Hewitt, 1957). Another example of an interesting metabolic effect of testosterone concerns ergothioneine. This sulphur-containing base which we isolated from boar semen a few years ago, and which occurs in high concentrations in the seminal plasma of certain species, such as boar, stallion, mole and hedgehog, is secreted in the male accessory organs (Mann & Leone, 1953; Leone, 1954; Mann, Leone & Polge, 1956; Heath, Rimington & Mann, 1957; Mann, Short, Walton, Archer & Miller, 1957). Ergothioneine occurs also, although in a much smaller concentration, in mammalian bone marrow and in blood corpuscles. A recent investigation, however, has shown that the blood ergothioneine level of female rats is consistently lower than that of males, but can be increased in the females by injections of testosterone (Mackenzie & Mackenzie, 1957).

Gonadotrophins

The control of male and female gonadal function by the pituitary gland depends chiefly on the activity of two gonadotrophins, the gametogenic or follicle-stimulating hormone (FSH) and the interstitial-cell stimulating or luteinising hormone (LH) Another source of gonadotrophin is the placenta, which produces chorionic gonadotrophin (CG); this is generally held responsible for the luteinising potency of pregnancy urine. In addition, a gonadotrophin, chiefly of the follicle-stimulating type, is present in the blood serum of the pregnant mare (PMS).

Newer trends in investigations on gonadotrophins involve much work on the influence of hypothalamus on the gonadotrophic activity of the pituitary gland (Harris, 1955) and on the chemical structure of the gonadotrophic hormones (Li, 1949; Morris, 1955). Those gonadotrophins which have been purified so far, are of glycoprotein nature and appear to depend on their carbohydrate moiety for biological activity. There is also a rapidly mounting flow of publications on the assay of gonadotrophins in the pituitary gland,

placenta, urine, and blood. Not only does it indicate the growing need for such assays but it reflects also serious shortcomings in the available techniques, due partly at least, to the lack of reliable chemical means for the separation of the two main gonadotrophic hormones, FSH and LH. Environmental conditions prevailing among the laboratory animals used for the bio-assay of gonadotrophins constitute another factor which can significantly influence the results; therefore, a good response from test-animals and reproducible dose-response curves may only be expected if the bio-assays are carried out under standardised experimental conditions (Frazer, 1956; Gilse, Nass & Kassenaar, 1956; Allison, 1956; Chance, 1956). A great deal still remains to be learned about the nature and function of gonadotrophins before the full physiological significance of this group of hormones is properly understood. However, new surprising data continue to accumulate, such as, for instance, the recent report that in complete contrast to pregnant mares which had been mated to stallions, in those mares which had been mated to jack-asses the level of PMS is practically *nil* (Bielanski, Ewy & Pigoniowa, 1956).

Another aspect of the physiology of gonadotrophins in want of further clarification is their relationship to nutrient requirements and to the general nutritional status of the animal.

This brings me to a further problem of animal reproduction, namely, the topic of:—

Nutrition in Relation to Reproduction

It is generally known that starvation or defective nutrition can upset the reproductive functions of man and animals alike. One of the earliest surveys of this problem is in the monograph by Jackson, on "The Effects of Inanition and Malnutrition upon Growth and Structure" (1925) and since then the subject has been repeatedly reviewed, notably by Biskind (1946); Hertz (1946); Samuels (1948); Russell (1948); Mason (1949) and Lutwak-Mann (1951). The growing interest in this field is well illustrated by the fact that the International Congress of Nutrition, held in July, 1957, in Paris, decided to devote to "Nutrition and Reproduction" an entire section, comprising amongst many others, contributions on the mineral requirements for reproduction, the rôle of vitamins, and the dietary importance of proteins and lipids for the normal functioning of reproductive processes (Kosterlitz & Campbell, 1957; Roche, 1957; Giroud & Lefebvres, 1957).

Remarkable progress was made in the domain of mineral studies on cattle, particularly on calcium, phosphorus, manganese and copper requirements. However, most of the results obtained by analyses of these metals suffer from a serious defect, namely they have been obtained on biological material which was deproteinised or ashed. It is worth remembering that most metals, and particularly those belonging to the category of trace elements, do not in fact occur or function in the animal body as free inorganic ions but form part of highly-active protein complexes, some of which, as for example, those of iron, copper or zinc, are endowed with definite enzymic activities. It is equally important, I think, to keep in mind the fact that a single metal can occur in several protein complexes, but of different biological activity, and that deficiency symptoms may be the outcome of a lowered content of one or several of these complexes. Iron, for example, occurs in the animal body in the form of protein compounds such as haemoglobin, myoglobin, catalase, peroxidase, the various cytochromes, ferritin, etc., and it is conceivable that a given deficiency may affect one, but not necessarily all, of these compounds.

Of the various vitamins, those belonging to the B-group, and also vitamins A and E appear to be particularly important for the normal functioning of reproductive processes. The need for an adequate supply of the vitamins of the B-group for fertility and foetal development was again emphasised in recent years by several investigators (Pfaltz & Severinghaus, 1956; Nelson & Evans, 1955, 1956; Ross & Pike, 1956). Further studies have also been reported on the most interesting but as yet obscure effect of both hypo- and hyper-vitaminosis A upon the incidence of malformations and upon the occurrence of reproductive disorders in rats, rabbits and cattle (Giroud, Gounelle & Martinet, 1957; Millen & Woollam, 1956; Jaskowski, Walkowska, Dobrowolska & Domanski, 1956). How complex, however, the vitamin influence may be, can best be deduced from a recent report by Woollam, Pratt & Fozzard (1957) who found that vitamin administration to rats exposed to a single dose of X-radiation early in pregnancy increased markedly the incidence of anophthalmia in the foetuses.

Protein and amino-acid deficiencies in relation to animal reproduction continue to receive much attention. In this respect a new but most promising line of research has been opened recently, pursued by Wolff (1957) and his pupils, who studied the influence of various amino-acids on the growth and differentiation of embryonic tissues in cultures under conditions *in vitro*.

My own interest in "Nutrition and Reproduction" centres on one particular aspect, namely the effect of underfeeding on the reproductive functions in the male. The first experiments in this direction were carried out on rats, in 1950 (Lutwak-Mann & Mann, 1950a, 1951) when it was shown that the secretory function of the male accessory organs in the rat can be reduced to a level almost as low as that of castrate animals, by restricting either the vitamin B intake or the total calorie intake. At the same time it was found that the secretory activity of such organs could be promptly restored by injections either of testosterone or of chorionic gonadotrophin, thus allowing the conclusion that the adverse effect of defective nutrition on rat accessory organs is due not to a primary lesion in the testes but rather to a failure in the pituitary mechanism which is needed to keep up testicular function. These experiments were next followed by a study of the effect of underfeeding on the genital functions in the bull (Mann & Walton, 1955): a mature bull had its daily food ration reduced to such an extent that it began to lose weight at a rate of about 6 kg. per week. After a 23-week period

of underfeeding the volume and sperm density as well as sperm morphology and concentration were not grossly affected. On the other hand, however, the secretory function of the seminal vesicles was severely reduced so that the level of fructose in ejaculated semen decreased by about 30 per cent. and that of citric acid by about 60 per cent. of the original level. A 25-week post-experimental period of recovery was required to restore to normal the secretion of fructose and citric acid.

Quite recently, we have been studying the influence of underfeeding on the onset of secretory activity and spermatogenesis in young bull-calves. For these experiments we used 3 pairs of monozygous twin-calves, of which one bull-calf was kept on a normal, and the other on a defective, diet (Mann & Rowson, 1956; Davies, Mann & Rowson, 1957).

At the very early age between 2 and 8 months the male calf is unable to yield semen in the normal manner. That difficulty, however, has been overcome successfully by the application of the electro-ejaculation method. Using the electro-ejaculator it was possible to obtain the seminal plasma which represents the male accessory secretions, at an age as early as 4 months, that is, some months before a bull calf can ejaculate semen in the natural manner or in response to the artificial vagina. By means of the electro-ejaculator the seminal plasma was thus collected at approximately two-weekly intervals throughout the whole experimental period, that is, up to the time when the experiments were finally terminated.

The appearance of fructose and citric acid which served as indicators of androgenic activity was considerably delayed by underfeeding. Whereas in the control twin fructose and citric acid were detected already at 4½ months of age, in the undernourished twin they appeared at 8½ months of age. Gonadotrophin, however, administered at an early age, even before the normal time of fructose and citric acid appearance, produced an immediate secretion of both substances. It would thus appear that underfeeding delays the onset of androgenic activity in the bull-calf not so much because the testes are unable to produce the male sex hormone, but rather owing to the lack of an adequate gonadotrophic stimulant to the testis from the pituitary gland.

In the normally-fed twin calf spermatozoa appeared in the semen about 4 months later than fructose and citric acid, *i.e.* at the age of 8½ months. In the underfed animal, on the other hand, they appeared only one month later than fructose and citric acid, *i.e.* at the age of 9½ months. Underfeeding appears, therefore, to delay the androgenic activity much more than the production of spermatozoa.

Concluding Remarks

This, of necessity, rather condensed survey of recent achievements in the field of animal reproduction will not, I hope, leave you with the impression that but little remains in this domain for the enterprising and ambitious research worker to accomplish in the future. The situation is, in fact, quite the reverse: of the problems which I have selected for the discourse, none can be regarded as truly solved, and a great deal more research will be required before we arrive at the mechanism underlying sex ratio, reversal and differentiation, the mode of action of sex steroids on the accessory organs of reproduction, or the way in which a nutritional deficiency affects reproductive processes in man and animal. To predict, however, which line of experimental approach is likely to turn out most rewarding or worthwhile, would be neither wise nor possible. The growing impact of physical and chemical techniques on biological research in general, appears to make highly probably further developments along bio-physical and biochemical studies. I would not wish to imply, however, that morphological methods are to be regarded as outmoded and thus less profitable. Recent developments, for instance, in electrone microscopy of the male and female gametes bear ample witness to the importance and fruitfulness of the descriptive approach. In my personal opinion, a judicious but at the same time bold and imaginative combination of several disciplines and techniques gives the best prospect and is likely to yield the most valuable results in animal reproduction as much as in any other field of biological research.

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The Chairman, Mr. W. C. Miller, in introducing the lecturer, said that Dr. Mann held an international reputation in a field which he had made peculiarly his own—the biochemistry and physiology of reproduction. Dr. Mann was Reader in the Physiology of Reproduction in the University of Cambridge and a Director of the Agricultural Research Unit of Reproductive Physiology and Biochemistry in Cambridge.

The Association was privileged in being able to hear an address by Dr. Mann on his own particular subject at a time when both animal production and reproduction were occupying a greater part of agricultural activities, and would occupy an even greater part in the future.

Dr. Mann then read his paper.

The Chairman said that most veterinary surgeons in practice were troubled with the grave problems of reproduction which beset the individual animal, male and female, and had acquired a considerable degree of expert knowledge in dealing with the problems which arose from day to day. Dr. Mann had placed before delegates some of the minutiae—the details of a biochemical and physiological nature, both normal and abnormal—and had brought that aspect of the work up to date. It would be fair to say that he had for some lifted a corner of the curtain which fell in front of the mystery of life. Had he done nothing else than give delegates a more healthy appreciation of the extreme complexity of the problems, that in itself would have been valuable and salutory. Dr. Mann had rightly stressed the need for more work, and it was gratifying and interesting to hear him include in the further work which was required not only the purely biochemical or biophysical techniques, but also the contribution which some of the less exploited techniques had still to make. It was with great pleasure that he proposed a hearty vote of thanks to Dr. Mann for his most interesting address.

The vote of thanks was carried by acclamation.

Bacterial Endocarditis of Cattle

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Introduction

THERE are several reasons for introducing this topic for discussion. Firstly, the general belief that endocarditis is rare among domestic animals, with the exception of the pig, is contradicted by an investigation of morbidity and mortality among cattle in South-West Wales during 1947-50, and by subsequent work at Cambridge. A second reason is that early diagnosis is often difficult and though most of the observations that I have to offer are on pathological aspects, these may offer explanations for some of the perplexities and suggest methods of approach in its diagnosis. Finally it is a fascinating disease and could possibly be of considerable comparative interest particularly to those more closely concerned with elucidating a similar condition occurring in man, about which a great deal has been written.

Definition and Classification

The essential definition of the term endocarditis is that it indicates an inflammatory affection of the endocardium, usually limited to the cardiac valves, but may extend over, or else primarily involve, the mural endocardium. Moreover, it appears from current text-books of human cardiology that it may also embrace similar affections of the great vessels (Endarteritis) (Wood, 1956). The arfection is generally, though not always, bacterial in origin.

It is customary in veterinary books to classify the condition into two main types, *viz.*, acute and chronic, with further subclassification of the acute variety into (a) acute simple, vegetative or non-ulcerative endocarditis, and (b) acute malignant, or ulcerative endocarditis. Chronic endocarditis is considered to be:—

(a) the permanent effect of the acute form;

(b) chronic from its outset, resulting from chronic infections such as tuberculosis or chronic swine erysipelas, or

(c) the manifestation of some toxic effects produced by various agents on the endothelium.

Generally speaking, in the acute form there are found formations of thrombi on the endocardium which may become exuberant vegetations that are soft and friable with a tendency to invade and destroy the underlying endothelium, occasionally resulting in perforation of the valve cusps. The inflammatory reaction is frequently intense. In the chronic form the lesions are mainly composed of fibrous tissue, are wart-like or verrucose in appearance and smaller than those found in the acute form.

In man an intermediate form is recognised and is by far the commoner variety. In this, known as subacute bacterial endocarditis, the vegetations are similar in appearance to those of the acute form, but there is present a varying degree of fibroblastic reaction with capillarisation indicative of organisation. These approaches to classification are considered to be artificial and the course of the disease and type of lesion produced are dependent upon the virulence of the causative organism and the resistance of the host. Since no clear division between the types can be discerned it has been considered better to regard them as one disease entity (Wood, 1956). It has to be realised that the chronic form can have had an acute phase and also acute exacerbation may occur during the course of the chronic condition.

A commendable alternative classification is that according to aetiology and two main types may thus be recognised, *viz.*, infective and non-infective endocarditis. When the aetiological agent has been identified the classification becomes more precise, *e.g.*, mycotic endocarditis, pneumococcal endocarditis. Recognition of the causal organism is exceedingly important nowadays since the effective use of the appropriate antibiotics has entirely changed the prognosis and clinical course of bacterial enodcarditis in man (Christie, 1953).

Review of Literature

Although reference has been made to the considered rarity of the condition, particularly by authors of veterinary text-books, search of the periodical literature reveals numerous reference to its occurrence in most kinds of both domestic and wild animals. Admittedly most of these are reports on sporadic, isolated cases considered worth while recording for interest's sake or as examples of mistaken diagnoses.

An extensive bibliography of references relating to endocarditis in horses, pigs, sheep, dogs, poultry and a variety of wild animals has been compiled but it is considered beyond the scope of the present article to refer to these more than is necessary to illustrate some comparative points.

From the periodical literature available to me it appears that the first reference to the condition in cattle is a case reported by Carlisle (1841) wherein he describes vividly ". . . the action of the heart resembled the clapper of a water-wheel and rendered my endeavours inadequate to judge of its motion." This article was followed by Gowing (1848), Shenton (1852), Gamgee (1857), Anon. (1859), Roberts (1881) and McFadyean (1889), all of whom described some clinical features and the discovery at *post-mortem* of endocarditis. Thomassen (1899) considered the condition to result from polyarthritis and Sheather (1911) described a case in which the endocarditis was present in association with a septal defect in the heart.

Since 1920 over 20 references to endocarditis in cattle have appeared. Since most of these will be mentioned later in the text it is only necessary to

mention a few at this stage. Winqvist (1945), John (1947), Morris (1949) and Kearney (1950) have all drawn attention to its not infrequent encounter, and recently Huhn and Müller (1955) have reviewed the literature concerning traumatic endocarditis. Brown (1955) described 6 cases of " 3-day Stiff-Sickness " in cattle that subsequently developed endocarditis.

The salient clinical features collected from these reports include: anaemia, jaundice, depression, loss of flesh, intestinal upsets such as rumenal tympany, scour, constipation, laboured respiration, pain, lameness, muscle tremor and recumbency, fever, abnormal heart sounds and rapid pulse rates, jugular distension and pulse, blindness, facial paralysis and other nervous derangements, and sudden death.

Material Examined

Material collected from a total of 40 cattle forms the basis of this paper. On 28 of these a full *post-mortem* examination of the entire carcases was performed by me, whereas the other 12 were necropsied by other veterinary surgeons who very kindly forwarded intact hearts, together with other organs when considered appropriate from 9 cases, and portions of valvular vegetations from the other 3 cases. They, furthermore, provided brief case histories for 15 animals and through their co-operation I was able myself to examine a further 6 animals *ante-mortem* on few occasions.

The bulk of the cases were encountered in South-West Wales and only 3 have been seen at Cambridge.

The observations presented in this paper include data on incidences, macroscopic and microscopic pathology, bacteriological examinations performed on blood during life and on various lesions found at *post-mortem* examination, haematology and urine examinations together with brief synopsis of the clinical features of the disease. Some of the pathological features will be reported in greater detail elsewhere.

Because the same examinations were not performed on all 40 cases the relevant details of the procedures are given in the section dealing with the particular aspects.

Incidences

Out of 610 unselected bovine carcases examined in three South-West Wales knackeries 24 were considered to have died, or been disposed of in a moribund condition because of endocarditis. This gives a proportional death rate of 3.93 per cent.

Comparable figures for some other diseases were as follows:—

Traumatic pericarditis	2.79 per cent.
Myocarditis	0.33 ,, ,,
Other heart conditions	0.98 ,, ,,
Johne's disease	4.42 ,, ,,
Pyelonephritis	3.44 ,, ,,
Mastitis	3.93 ,, ,,
Tuberculosis	7.21 ,, ,,
Salmonellosis	3.93 ,, ,,
Piroplasmosis	5.57 ,, ,,
Complication of parturition (including metritis)	9.30 ,, ,,

There were five other knackeries operating in the area and from records kept by these and the above 3 the calculated minimal crude death rate from all causes in a total mid-year cattle population of nearly 300,000 came to 132.5 per 10,000 head per annum.

Assuming that no great variation existed in the causes of disposal into the knackeries situated in various localities within the area, estimates for the crude death rate, due to heart diseases, per 10,000 head per annum appear as follows: endocarditis 5.2, traumatic pericarditis 3.7, myocarditis 0.4, other miscellaneous heart conditions 1.5, and collectively for all heart disease 10.8.

Over the same period 30 out of 50 veterinary surgeons practising in the area kept records of their daily work. From this information it has been estimated that the crude morbidity rate for cattle amounted to 1,537 per 10,000 head of the population (c.f. Grunsell's morbidity rate of 186/1,000 head derived from a similar approach (Grunsell, 1955), and the estimated crude morbidity rate for endocarditis came to 0.31, for traumatic pericarditis to 0.57, other miscellaneous or unclassified heart disease to 0.4, giving a total morbidity rate for all cardiac disorders of 1.28 per 10,000 head of cattle population per annum respectively.

There is obviously a great discrepancy between the two estimates. It may be that a proportion of the cases entering the knacker's yard were not attended during life by veterinary surgeons; this was definitely so in one case in which the sole history was that of collapse whilst being brought in for milking with death within a few minutes.

The most probable and important explanation for the discrepancy is that of misdiagnosis. This aspect will be discussed later but it apparently supports the statement by Mousso quoted by Wallis Hoare (1915), that the affection is often overlooked and only discovered at *post-mortem* examination.

Whatever the cause of the discrepancy, the fact remains that the porportional death rate indicates the condition to be as common and important as some other well-known and more readily diagnosed diseases.

Figures giving comparable incidence in the material examined at their Departments of Pathological Anatomy have been provided by Winqvist (1945) and Schornagel (1936). The former found the proportional death rate for endocarditis to be 0.72 per cent. and the latter 2.4 per cent. of all cattle carcases examined by them.

Recently Peck (1957) in a survey which included the *post-mortem* examination of 300 cattle at a knackery in Devon found 4 cases of bacterial endocarditis, a proportional death rate of 1.33 per cent.

Age Incidence

The age distribution in the total of 40 cases is presented in Table I.

Withers (1957) has shown that there is a marked rise in the amount of total sickness and mortality with increasing age in dairy herds and it is therefore pertinent to consider whether endocarditis contributes proportionally to this increase in mortality. It is

TABLE I

Age in years	under 1	1–2	2–3	3–4	4–5	5–6
Number of cases	1	3	3	3	5	3
Per cent. of the total number ...	2·5	7·5	7·5	7·5	12·5	7·5

Age in years	6–7	7–8	8–9	9–10	10-over	Not stated
Number of cases	5	2	2	2	6	6
Per cent. of the total number	10·0	5·0	5·0	5·0	15·0	15·0
		30 per cent.				

possible to do so in the 24 cases that were encountered in the unselected material mentioned previously and it will be seen from Table II that whereas a larger number of cattle over 7 years of age were affected with endocarditis, proportionally it does not contribute more towards causation of death or disposal in the older cattle than in any other age group.

TABLE II

AGE DISTRIBUTION IN 24 CASES OF ENDOCARDITIS ENCOUNTERED IN 610 CARCASES EXAMINED AT 3 KNACKERS' YARDS

Age in years	Number of endocarditis cases	Total number of carcases examined in each group	Endocarditis cases as a per cent. of total carcases in each group
Under 1	0	18	0
1–2	3	56	5·3
2–3	1	58	1·7
3–4	2	43	4·6
4–5	3	63	4·8
5–6	2	48	4·2
6–7	3	56	5·3
Over 7	9	201	4·5
Not stated	1	67	1·5
Totals	24	610	3·93

Breed incidence

In South-West Wales the predominant breeds of cattle are Shorthorn and Friesian and as expected the majority of the cases encountered involved these two breeds. Of 30 animals for which the breed type was recorded, 15 were Shorthorn, 11 were Friesian and the remainder comprised 2 Welsh Black, 1 Jersey, 1 Ayrshire and 3 of indeterminable cross-breeding.

Sex incidence

Out of the total number of 40 cases, 2 were bulls, 1 was a steer and the remaining 37 cases were females. The farming practice in the area is predominantly dairying and it is to be expected that very few males or steers were at risk compared with females.

It is interesting to note that in Ireland Kearney (1950) found in his series of 14 cases of bovine endocarditis 8 to be steers, 4 females and 1 bull.

Seasonal incidence

To check on any evidence of seasonal incidence, analysis has been made of the 610 unselected carcases examined at the knackeries, and because of the gross seasonal fluctuation in the intake of animals into these yards Table III has been compiled so as to correlate the monthly encounter of endocarditis cases with the monthly total of carcases examined.

TABLE III

CORRELATION OF THE INCIDENCE OF ENDOCARDITIS WITH THE MONTHLY TOTAL OF BOVINE CARCASES EXAMINED

Month	Monthly total of cattle carcases examined	Number of endocarditis cases	Per cent. of monthly total	Quarterly distribution percentage of the 24 cases
January ...	31	2	6·45	16·7
February ...	42	2	4·88	
March ...	53	0	0	
April ...	102	3	2·94	20·8
May	64	3	1·56	
June	54	1	1·82	
July	46	3	6·67	25·0
August ...	26	0	0	
September ...	49	3	6·25	
October ...	66	4	6·06	37·5
November ...	41	3	7·30	
December	36	2	5·71	
Total ...	610	24		100

It appears from this table that there exists a greater tendency for a higher incidence of endorcarditis during the latter half of the year but probably the numbers are statistically too small for any positiveness on this point.

Post-mortem Appearances

The remarks on this section are based on findings in the examination of 28 intact carcases.

External Appearances

The carcases of 19 animals were grossly emaciated, 5 were in fair and the other 4 in good bodily condition. In some of the emaciated cases the skins were deeply ulcerated with sloughing, particularly over the prominences. This was considered to indicate long periods of recumbency before death. Frequently the hind quarters were grossly soiled with faeces.

The visible mucosae were pallid in most of the carcases but in four cases they were frankly jaundiced.

Internal Appearances

Pronounced anasarca was present in twelve carcases and ranged in severity from slight oedema in the brisket and submaxillary regions to involvement of all the lower abdomen, back as far as the perineum, and in two instances spread down the legs over the hocks and knees. Another feature of these cases was marked hydrothorax and ascites associated with thickening of the mesentery, abomasal, intestinal and gall bladder walls. The mucosal folds of the abomasum and also the colonic and caecal walls

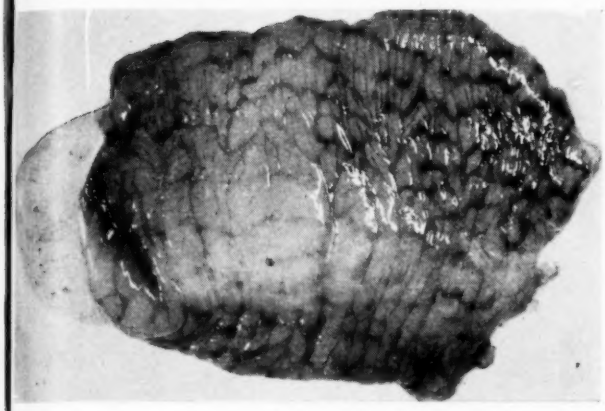

FIG. 1.
Gross oedema of the caecal wall.

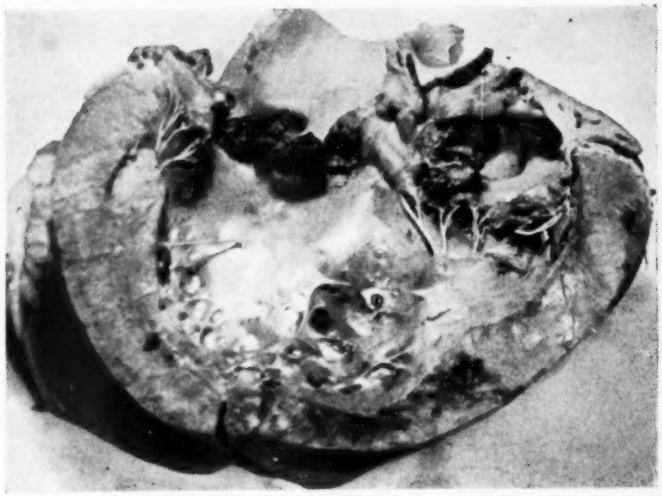

FIG. 2.
Heart showing gross verrucose lesion on the aortic valve cusps and smaller ones on the left auriculo-ventricular valve. Note also the myocardial degeneration on the right cut surface.

FIG. 3.
Longitudinal section of right auricle. A very large verrucose lesion on tricuspid valve causing a severe distortion of the heart contour.

FIG. 4.
Vegetations on right auriculo-ventricular valve. Note the almost complete occlusion of orifice and the infiltration of fibrous tissue into the substance of interventricular septum on the left.

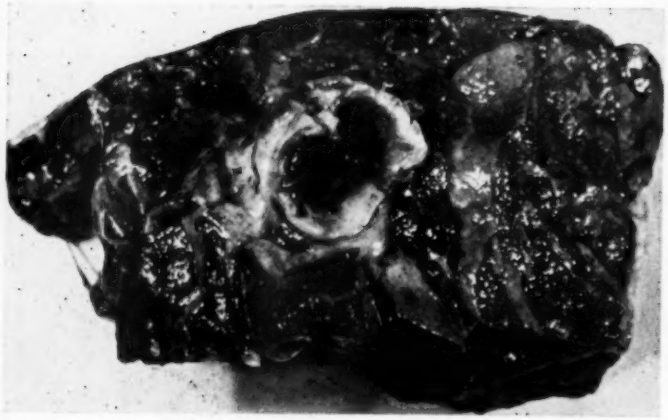

FIG. 5.
Picture of portion of lung showing embolus lodged in a large branch of the pulmonary artery.

FIG. 7.

Superior aspect of heart with auricular walls trimmed off to show verrucose lesions on both auriculo-ventricular valves. Aortic and pulmonary valves free from macroscopic lesions.

FIG. 6.
Photograph of the kidneys from a case of *C. pyogenes* endocarditis. Note the pale infarct involving several lobes on the lower pole of the right kidney and the distinct pyaemic abscesses. Few haemorrhagic foci are also visible in the right kidney giving it a "flea-bitten" appearance.

FIG. 8.
Dorsal aspect of heart trimmed as above showing gross lesions on aortic valve. Smaller lesions on both auriculo-ventricular valves.

FIG. 9.
Photograph of mural verrucose lesion in the left ventricle.

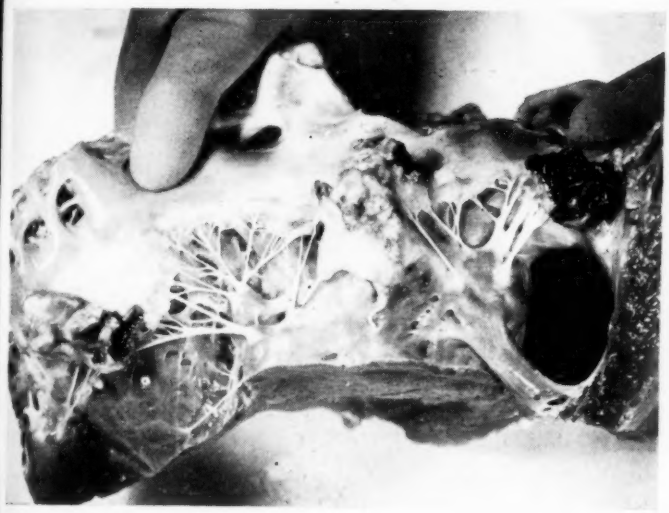

FIG. 10.
Vegetations on the three cusps of the right auriculo-ventricular valve. Note the variation in colour between those on the different cusps.

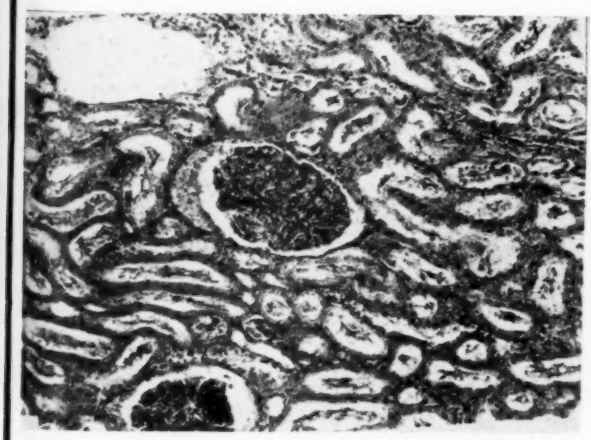

FIG. 12.
Section of kidney cortex illustrating early crescent formation in the central Bowman's capsule.

FIG. 13.
Classical kidney infarct.

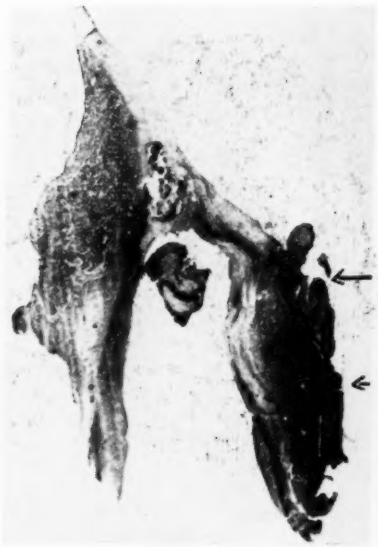

FIG. 11.
Section of mitral valve cusps showing colonies of bacteria located in the dark zone between arrows.

were often up to ¾ inch thick which, on cutting, oozed copious quantities of clear oedema fluid from the surfaces. (Photograph 1.)

Cardiovascular System

Heart

Pericardium. There was increased quantity of transudate in the pericardial sacs of all cases that showed oedema elsewhere. In two animals there was widespread fibrinous pericarditis with adherence of the visceral and parietal layers with very little exudation. No evidence of a foreign body could be found and neither was the pericarditis so severe as that customarily encountered in traumatic pericarditis. In another two cases the pericardial adhesions were localised to sites apposed to gross vegetation on the mural endocardium and were probably resultant to a spread across the myocardium. The lesions in the remaining two hearts showing pericarditis were recent and mild with fibrin deposition confined to the visceral layers surrounding the base of the heart and origin of the great vessels.

Myocardium. Infarction of the myocardium was observed in three hearts. In one case it was very extensive involving approximately the apical half of both ventricles and emboli were found in the left coronary artery. The infarctions in the other two were circumscribed and confined to the posterior wall of the left ventricle with emboli again present in the posterior branches of the left coronary artery. In these three cases the gross endocardial vegetations were present either on the aortic valve or in the left ventricle. (Photograph 2.)

Endocardium. The location and gradation according to size, of the endocardial vegetations were recorded but full consideration will be given to these later, when discussing the more composite material.

Atheroma-like plaques were visible on the endocardium of the left auricle and on the intima of the aorta in one case.

Shape and size of the heart. A variable degree of distortion was apparent in most of the hearts examined. This was due partly to myocardial hypertrophy and/or dilatation of one or more chambers, but the most marked distortion resulted from a combination of dilated and hypertrophied right auricles, a bulging at the level of the tricuspid orifice by large vegetations affecting that valve, and some degree of wasting of the anterior wall of the right ventricle. (Photograph 3.)

Some hearts were obviously enlarged and heavier than normal, one weighed 9¼ lb., and another nearly 8 lb. This heaviness did not result purely from hypertrophy of the myocardium since the vegetations themselves would have contributed considerably towards it.

Posterior vena carva. In one case the posterior vena cava showed gross distension caused by thrombus, originating from a large abscess lying between the vessel and the liver. The thrombus extended forward to protrude into the right auricle, spreading over the mural endocardium of that chamber and the posterior cusp of the tricuspid valve, with vegetations present on the other cusps.

Respiratory System

Lungs. Passive venous congestion was present in 12 cases and in 10 of these brown induration was well manifested.

Multiple infarctions located on both surface and in the substance of the lungs were seen in four cases, and in some instances the causative emboli were frequently lodged in relatively large branches of the pulmonary arteries. (Photograph 5.)

Small abscesses were seen in 6 sets of lungs but were multiple in three only.

Pleura. The pleurisy observed in three cases was never extensive and in two was localised to the visceral pleura overlying abscesses or infarcts, whereas in the other it was mild with fibrinous deposits on both visceral and parietal layers.

Digestive System

Gastro-intestinal tract. In five animals there existed a catarrhal enteritis, and in another four animals multiple shallow, discrete mucosal ulcers were seen on the abomasal folds or in the jejunum. These ulcers were frequently covered by necrotic caps which separated readily revealing haemorrhagic bases.

Liver. Gross enlargement of the liver was apparent in the livers of 11 animals which, in one instance, weighed 37 lb. These livers presented the classical nutmeg appearance of passive venous congestion. Cirrhosis was seen alone, or in conjunction with venous congestion, in 14 cases. In 12 of these it was coarse, biliary in distribution and associated with fluke infestation. Abscesses in the bile ducts were present in 3. The fibrosis in the other two was fine and diffuse similar to that caused by ragwort. Telangiectasis was seen in two livers.

Spleen

Gross engorgement and swelling were seen in the spleens of five animals.

Urogenital System

Kidneys. The most prevalent finding was that of multiple small haemorrhagic foci scattered over both the capsular and cut surfaces of the kidneys. Such kidneys, commonly encountered in subacute bacterial endocarditis of man, are descriptively referred to as being "flea bitten" and, as will be mentioned later, are indicative of focal embolic nephritis. These haemorrhages were the sole macroscopic finding in some kidneys but in others were frequently associated with infarctions of various sizes and age. Some of the infarctions were really gross involving 5 or 6 lobes of the kidney. (Photograph 6.)

It is also interesting to record that in the cases of endocarditis caused by the more pyogenic organisms, abscesses were found scattered throughout the cortices of the kidneys.

Pale, mottled and grossly swollen kidneys, suggestive of subacute nephritis, were observed in four cases.

Uterus. It one instance a collection of pus lay free within the horn of a gravid uterus, whilst the placenta was retained in another two recently calved animals.

Skeletal System

In the limbs of 7 carcases there existed pronounced arthritic changes. The joints most commonly affected were the hip, stifle and hock of the hind limb, and the shoulder and elbow joints of the fore limb. The lesions apparently commenced as a softening of the central cartilages followed by fissuring and progressive destruction with eburnation of the underlying bone and in the more severely affected joints the erosion of the cartilage was so extensive that bone articulated direct with bone. There did not appear to be any gross changes in the synovia and neither were the periarticular tissues affected. Numerous attempts at culturing organisms from these joints proved fruitless.

However, in the case of a young calf that had a history of joint-ill the arthritis was purulent in nature and was so wide-spread as to involve amongst others the occipito-atlantal articulation; from the joints of this calf organisms were isolated, similar to those found in the cardiac vegetation.

Comments on the Gross Morbid Anatomy of these 28 Cases

It is apparent from these findings that the lesions encountered were divisible into two main classes.

The oedema, chronic venous congestion, enlargement of the spleen, and the jaundice can be attributed to heart failure, whereas the other lesions such as the infarction in the various organs, the "flea bitten" kidneys, pyaemic foci in the kidney and lung resulted from embolism.

However, it is difficult to assess the nature of the joint lesions. One of the earliest clinical signs in a number of cases in this series and in that recorded by other workers is that of joint lameness or polyarthritis. It may be that they were caused by embolic occlusion of the terminal arterioles, or else that they resulted from allergic reactions analogous to that occurring following the injections of serum. Moreover, they are not peculiar to endocarditis since they are frequently found alone, causing disposal due to the so-called joint rheumatism of aged cattle, or else in association with a variety of diseases such as mastitis, Johne's disease, myocardial abscesses, and atheroma like affections of the endocardium or vascular endothelium.

The "Vegetations"

Gross appearances. The external appearance were very similar in all cases though they varied considerably in size within the same heart from the early, barely visible, nodules approximately 1 to 2 mm. in diameter situated along the line of apposition of the valve cusps to the large cauliflower growths that almost occluded the orifices. In these larger vegetations fusion of the cusps was common, and, moreover, the cusp outline would have disappeared within a mass that encroached over the contiguous endocardium and spread down the chordae tendinae. The irregular surfaces were crumbly but the bases were firmly attached to the endocardium. (Photographs 4, 7, 8 and 9.)

In colour the surfaces were generally greyish white but frequently a recent deposition of blood and fibrin gave them a dark red coloration. (Photograph 10.)

Microscopic appearances. Three main zones could readily be recognised in the larger lesions. A superficial zone composed of fibrin and varying numbers of red and white blood cells merged into an intermediate zone of fibrin with numerous colonies of bacteria embedded within it, and frequently separated from a basal zone by an extremely cellular layer of polymorphs and macrophages. The inner, or basal zone, was composed outwardly of fibro blastic tissue showing moderate capillarisation and merged into an organised fibrous layer blending with the underlying myocardium. (Photograph 11.)

Comments. The degree of organisation encountered in these vegetations stimulates a postulation that the onset of endocardial infection occurred in some cases long before the manifestation of obvious signs of ill health, and that the first attendance by the veterinary surgeon coincided with the terminal phases when cardiac embarrassment had become sufficiently pronounced to inconvenience the animal and render ill health noticeable.

It is also almost unbelievable that in some instances, wherein very large vegetations were present, the duration of illness recorded should have been so brief. This is notably emphasised in the one cow which, more or less, dropped dead without exhibiting any previous symptoms. This was the case mentioned earlier wherein gross myocardial infarction was found on autopsy.

TABLE IV

RELATIVE SIZE AND DISTRIBUTION OF THE VEGETATIONS

Relative size of vegetation	Location of valvular vegetations				
	Tricuspid	Pulmonary	Mitral	Aortic	Parietal endocardium
+++	19	5	5	4	3
++	3	—	8	—	2
+	6	5	11	6	13
—	8	26	12	26	18
Number of times each site was affected	28	10	24	10	18
Per cent. as largest lesion	52·8	13·9	13·9	11·1	8·3
Location as per cent. of the 36 hearts	77·8	27·8	66·8	27·8	50·0

Key :—

+++ = Largest lesion, frequently almost occluding the valve orifice.

++ = Intermediate lesion, approximately bean sized.

\+ = Small discrete lesions up to size of pea. In case of parietal endocardium it indicates spread from a valvular lesion.

— = Absence of macroscopic lesions.

Distribution of Vegetations

The relative size and distribution of the vegetations in the 36 intact hearts examined is presented in Table IV. It is realised that size of lesion does not necessarily indicate the primary focus of endorcardial infection; it would be expected nevertheless, that the degree of occlusion of the valvular orifice should have influenced the clinical picture.

Simultaneous affections of more than one valve was present in about two-thirds of the hearts and Table V provides an analysis illustrating the relevant findings.

TABLE V
AFFECTIONS OF ONE, OR COMBINATION OF VALVES

Name of valve	Number of times	Totals	Per cent. of the 36 hearts
Single valve affections			
Tricuspid	6		
Mitral	3	10	27·8
Pulmonary	1		
Double valve affections			
Tricuspid and nitral	9		
Tricuspid and pulmonary ...	1		
Tricuspid and aortic ...	1	13	36·1
Mitral and aortic	1		
Pulmonary and aortic	1		
Triple valve affections			
Mitral, tricuspid and aortic ...	4		
Mitral, tricuspid and pulmonary	4	8	22·1
All four valves	3	3	8·3
Mural endocardium as solitary site	2	2	5·6

It is apparent from these tables that the tricuspid valve was the most frequent location of the vegetations. Next in sequence was the mitral but this valve was the seat of the largest lesion in 5 hearts only. The pulmonary and aortic valves were each affected in 10 hearts but were the seat of gross vegetations in 5 and 4 hearts respectively. Pure mural or parietal endocarditis was encountered twice and the largest vegetation was located here in another heart. In the remaining 15 hearts the parietal lesions had resulted from spreading of the valvular vegetations.

It is convenient at this stage to compare the distribution of vegetations with those recorded by Winqvist (1945), Schornagel (1936), Ackernacht (1922). There is a similar tendency exhibited by all these series in that the right side of the heart was more frequently involved than the left side but the proportion of hearts showing simultaneous involvement of both halves was much higher in my series than reported by the other workers. However, Kearney (1950) found the mitral valve to be affected in 7 of the 14 hearts which he examined. Table VI has been compiled to illustrate this comparison.

Another contrasting feature between Winqvist's findings and mine is the frequency with which the parietal endocardium appears as the sole site of endocarditis. Twenty-eight of the 58 hearts which

TABLE VI
COMPARISON OF DATA RELATING TO DISTRIBUTION OF LESIONS

	Number of hearts examined	Per cent. of the hearts showing lesions in the various sectors: Left heart	Right heart	Left and right heart
Schornagel (1936)	90	30·0	42·4	27·6
Winqvist (1945)	58	24·1	51·7	24·1
*Kearney (1950)	14	50·0	14·3	35·7
*Ackernacht (1922)	39	12·8	56·4	30·8
Present series (1957)	36	13·9	25·0	61·1

* The data recorded by Ackernacht and Kearney refer to valvular lesions only.

he examinaed showed lesions involving one sector only, and in 14 of these the vegetations were present on the parietal endocardium whereas, in my series, affections involving one site appeared in 12 of the 36 hearts and were purely mural on 2 occasions only. No precise explanation for these discrepancies can be offered apart from the variation between the causal organisms isolated in the 2 series, and that in 3 of his cases of mural endocarditis, the vegetation overlay primary myocardial abscesses.

Histological Appearance of Macroscopically Abnormal Kidneys

Microscopic examination of sections of such kidneys revealed a number of changes affecting the glomeruli, tubules, interstitial tissue, and the blood vessels.

The glomerular changes observed included acute haemorrhagic glomerulo-nephritis and subacute glomerulo-nephritis manifested in all its stages (Photograph 12). The other change noted appeared consistent with the so-called Lohlein-Baehr lesion or focal embolic glomerulonephritis. The embolic nature of this latter condition is disputed and should possibly be more correctly referred to as focal necrotising glomerulo-nephritis (Allen, 1952).

The epithelium of the tubules frequently showed degenerative changes and deposition of haemosiderin with or without blood casts in the lumen. Occasionally infected casts contained within the tubules were associated with peritubular reaction.

In the kidneys of those cases from which *C. pyogenes* or Staphylococcus was isolated, multiple abscesses of varying sizes were apparent in the glomeruli, tubules, and interstitial tissue of the cortex.

The blood vessels in a number of sections showed subintimal fatty-degeneration frequently accompanied by proliferative changes in the media and hypertrophy of the vessel wall.

The histological appearance of the infarcts presented classical features and requires no further elaboration. (Photograph 13.)

Comments

The nature of these renal lesions is of 2-fold significance. Firstly, the extent of glomerular damage in some cases was sufficient to have at least aggra-

vated, if not precipitated, the development of oedema.

Secondly, the extensive transudation of proteinoid fluid and blood into the Malpighian capsules, with their passage down the tubules, indicates that proteinuria and haematuria should have been present in these cases during life. This was so in 6 cases on which urine analyses were performed on 1 or more occasions. It remains to be seen whether similar renal lesions exist in some other cardiac conditions that could be mistaken clinically for endorcarditis.

Bacteriological Examinations

Direct cultures from several sites in one or more vegetations in each of 38 hearts were made onto horse-blood agar plates which were incubated aerobically and anaerobically at 37° C. for periods up to 1 week.

In 36 cases the primary cultures were usually pure but in 2 they were grossly contaminated and had to be discarded.

Where obvious lesions existed elsewhere in the body, cultures were made from those sites, and in the vast majority they yielded organisms identical to those isolated from the heart lesions.

Further corroboration of the causative authenticity of the organisms isolated was accomplished by finding in histological sections of the vegetations, stained by Jensen's modification of Gram's stain, morphologically similar bacteria occurring intracellularly or in colonies in the more active areas of the lesions.

The results of these bacteriological examinations were as listed in Table VII.

TABLE VII
ORGANISMS ISOLATED FROM VEGETATIONS OF 40 HEARTS

Bacteria isolated	Number of cases
Alpha haemolytic streptococci	20
Beta haemolytic streptococci	2
Streptococcus viridans	1
Anaerobic streptococcus	1
Alpha haemolytic streptococcus and *E. coli* ...	2
" " " and *C. pyogenes* ...	1
Corynebacterium pyogenes	4
Diphtheroid species	2
Micrococcus species	1
Haemolytic staphylococcus aureus	2
Grossly contaminated or no culture...	4
	40

It soon became evident that the predominant causative organisms were α- or non-haemolytic streptococci which showed a marked general similarity in their cultural characteristics. The last 16 strains of these streptococci were examined more extensively, and I wish to record here the generous assistance given by Dr. Stableforth and other members of his staff at Weybridge. The cultural characteristics, heat resistance, and fermentation reactions of the 16 strains resembled those of the enterococcus group of streptococci. Some liquefied gelatin and with the other reactions noted could be classified as *Str. liquifaciens* whereas those that did not liquefy gelatin could be considered as being *Str. faecalis*. Difficulty was encountered in grouping some of them serologically, but recently Dr. S. D. Elliott, using probably more potent sera, found them all to be Group D streptococci and moreover that they fell into 2 distinct types. Further details of his findings on these and some strains of Group D streptococci isolated from other sources are included in a brief contribution prepared by him for the discussion. No correlation existed between this serological type differential and that according to gelatin liquefaction.

As can be seen from Table VII a streptococcus was isolated either pure or in association with other organisms from 27 hearts and *Corynebacterium pyogenes* on 5 occasions. Though full examinations were not performed on the earlier strains of α-haemolytic streptococcus it is considered probable that they also were enterococci.

A relatively long list of causative organisms can be compiled from the reports of previous authors. Hutyra, Marek and Manninger (1946), quoting various workers, list *C. pyogenes*, *C. renale*, streptothrix, streptococcus, staphylococcus, and mycobacterium tuberculosis as causing endocarditis of cattle. To these can be added *E. coli* (Udall, 1954), diplococci, necrobacillus, and B. pseudo-tuberculosis ovis (Winqvist, 1945), and *Erysipelothrix rhusiopathiae* (Roemmale, 1952).

Winqvist (1945) reported *C. pyogenes* to be the predominant organism in his series of 41 affected hearts examined bacteriologically, having isolated it on 28 occasions and a streptococcus from 7 hearts. Kearney isolated streptococci from all his 14 cases, but he and Winqvist omitted to refer to the type nature of the streptococcus. Other authors who have reported streptococci as causative organisms include Peterson (1934), Mitchell *et al.* (1938), Morris (1949), O'Malley (1950), and John (1947). Peck (1957) reports the isolation of streptococcus viridans, a mixture of streptococcus faecalis and coliforms, and *C. pyogenes* from each of 3 affected hearts respectively.

The enterococci have generally been looked upon as harmless to both man and animals and numerous references are available demonstrating their occurrence as members of the normal flora of various regions in a number of species.

In normal healthy cattle Francis (1941) demonstrated enterococci in the tonsils and vagina and Simeoni (1949) examined 75 strains isolated from faeces of such cattle and found them to fall into 2 types, namely *Str. faecalis* and its variant *Str. liquifaciens*. As far back as 1926 Orcutt found enterococci in the digestive tract of both normal and scouring calves.

Nevertheless they have been incriminated as causative of mastitis in cattle (Torrey & Montu, 1936; Plummer, 1941; Auld & Parker, 1947).

In other species of animals they have been considered as the cause of endocarditis, *e.g.* lambs (Jamieson & Stuart, 1950) and pigs (Hont & Banks, 1944).

Recently, emphasis is placed on their contribution to bacterial endocarditis of man which, according to various authors, amounts to between 4 and 20 per cent. of the cases of coccal endocarditis (Bing, 1953). Furthermore, they can cause affection of previously normal heats, and enterococcal endocarditis is notoriously resistant to therapy (Logue & Tomlin, 1956).

Source of Infection

It is believed that bacterial endocarditis usually develops secondary to infection elsewhere in the body. The primary focus may be readily recognised and even dominate the clinical picture until late in its course. Examples of this were provided by those cases following upon metritis, mastitis, and septic joints. In one case there was a large abscess located between the posterior vena cava and the liver.

However, a primary focus was not apparent in the majority of cases or else it was difficult to ascertain whether abscesses such as were observed in the liver or lungs were primary or secondary to the endocardial lesions.

A heavy infestation of livers by fluke is commonly encountered in slaughter cattle in South-West Wales, and of the 610 bovine carcases examined in the knackeries approximately 60 per cent. showed fluke affection. In 12 of the endocarditis cases this was so and it appears feasible therefore that there may be an association between fascioliasis and endocarditis. This has been previously suggested by Zwijnenberg (1933) who also observed a decrease in the incidence of endocarditis following appropriate treatment of fluke disease in cattle. It appears a reasonable supposition that fluke cercariae migrating from the intestines into the liver could carry enteric organisms with them and that the purulent cholangitis frequently encountered in affected livers could easily act as focus of infection. Soulsby (1957) frequently isolated α-haemolytic streptocci and paracolon-bacilli from heavy fluke-infested livers of cattle at an Edinburgh abattoir whereas from a few nomal contol livers no such organisms were isolated. However, one snag with this postulation is the apparent absence of endocarditis in sheep in the same areas. Lacerations anywhere along the digestive tract or mucosal ulcers in the abomasum could also contribute towards bacteraemia by intestinal organisms in cattle.

In man bacteraemia by α-haemolytic streptococci frequently follows dental operations (Okell & Elliott, 1935) and tonsillectomy (Elliott, 1939a) and moreover these operations were the antecendent history in about 22 per cent. of the subacute bacterial endocarditis of man studied by Elliott (1939). No corresponding findings have as yet been described in cattle although it is possible that normal or abnormal tooth shedding might be associated with bacteraemia.

Conditions such as lacerations of the genital tract during calving, retention of the afterbirth, mild infection of the sinuses, following dehorning, post-castration wounds could well be conducive to bacteraemia, and since the enterococcus is not normally associated with gross purulence these local infections may not appear important.

In the continental literature there have appeared a few references to traumatic endocarditis arising from piecing of the myocardium by ingested foreign bodies such as needles and wires. The endocarditis is invariably associated with myocarditis and pericarditis (Diernhofer, 1946; Mussill, 1946; Huhn & Müller, 1955).

Pathogenesis

In man the malady commonly affects valves that are already abnormal as a result of damage acquired during infections such as rheumatic fever or pyphilis, or else those congenitally malformed or in hearts with other congenital defects. The exact mechanism of invasion is, however, not certain. Human heart valves are normally avascular and the evidence for surface implantation of the bacteria is strong (Harper, 1941). Damage to the endothelium is a prerequisite for such implantation and the various theories related to its development are too numerous to be discussed here (see Kerr, 1955).

The not infrequent finding of endocarditis in cattle following foot-and-mouth disease (Winqvist, 1945) and "3-day Stiff Sickness" (Brown, 1955) is probably explained by endothelial reaction in the valve cusps caused by the viral infections predisposing to bacterial implantation.

It has been demonstrated repeatedly that a high degree of immunity against a specific organism predisposes to endocardial infection by that organism. This is particularly well exemplified by its frequent encounter in horses kept for the produciton of hyperimmune serum (Wadsworth, 1918-1919; Winqvist, 1945).

In most domestic animals—cattle included—blood vessels occur normally in the heart valves (Harper, 1941) and primary embolism can thus be considered as a factor in the genesis of endocarditis in these species.

Although the full histological examination of the hearts in this series has not been completed, evidence for both surface implantation and intravalvular embolism is apparent in a number of sections of the valve leaflets.

Clinical Features

The satisfactory assessment of the full course of a disease requires a comprehensive series of examinations over a sufficiently prolonged duration. This was not possible under the conditions of this investigation but the brief clinical histories provided by other veterinary surgeons who attended 15 of these cases and the personal examination of 6 animals make it possible to collate a number of features which are presented in Table VIII. It is apparent that most of the symptoms and signs recorded are similar to those already described by the other workers mentioned in the earlier survey of the literature. However, some of the features warrant further elaboration and for convenience are considered under definite headings.

Onset and Duration of Illness

The clinical features recorded are varied and numerous and so occasion difficulty in portraying what

TABLE VIII

COLLATION OF THE CLINICAL FEATURES OF 21 CASES OF ENDOCARDITIS

Case No.	Initial illness or symptoms	Duration of illness	Abnormality of gait or posture	Gastro intestinal symptoms	Cachexia	Character of visible mucosae	Oedema	Dehydration	Respiratory distress	Cardio Vascular System: Pulse rates/min.	Cardio Vascular System: Heart sounds	Cardio Vascular System: Venous engorgement or pulsation	Pain	Temperature (°F.)	Other symptoms	Clinical Diagnosis
13	Mastitis	3 weeks	—	—	—	—	—	—	—	94·102 130	—	—	+	104	—	Traumatic reticulitis
15	Anorexia and respiratory distress	3 weeks	Arched back	Scour	+	Jaundice	—	+	+	Fast and irregular	—	Jugular pulse	+	105.102	—	Endocarditis
16	Anorexia constipation	1 month	Fatigue	Atony of rumen	—	—	—	—	+	Fast and irregular	Muffled	—	—	105.102	—	Traumatic reticulitis
18	Fatigue	3 months	Lameness	Atony of rumen	—	—	+	—	—	—	—	Jugular pulse	—	102.103	—	Endocarditis
19	Scour	1 month	—	—	—	—	+	—	—	Fast	Muffled	Jugular pulse	+	104	—	Traumatic pericarditis
20	Collapse and death	—	—	—	—	—	—	—	—	—	—	—	—	—	—	
21	Recumbency	—	—	—	—	—	—	—	—	—	—	—	—	—	—	Dislocated hip
22	Septic hock	—	Lameness	—	—	—	—	—	—	100	—	—	—	—	—	Endocarditis
24	*Post-partum* haemorrhage metritis	3 months	Lameness	Atony of rumen and intestines Anorexia	+	—	+	—	+	120	—	Mammary and jugular pulse	—	105.107 103	—	Endocarditis
25	Respiratory distress	2 weeks	Stiffness and recumbency	—	—	Jaundice	+	—	—	—	—	—	—	104	—	Pneumonia
30	Fatigue	Several months	Stifle lameness	Constipation	+	Pallor	+	—	+	80·96 92·88	Very loud	Jugular pulse	+	101.102 103.102	Muscular tremor	Endocarditis
33	Stiffness	2 weeks	Stiffness	+	+	Jaundice	—	+	+	80	No murmurs	Jugular pulse	+	105.102	—	Endocarditis
34	Septic fetlock	2 months	Septic knee and fetlock	Anorexia	+	—	+	—	—	100	No murmurs	Mammary and jugular pulse				
35	Loss of condition	3 weeks	Stifle lameness	Melaena	+	—	—	—	—	Rapid	—	—		104.105	Muscular tremor	?
36	Loss of condition	5 weeks	—	Atony of rumen	—	—	+	—	—	80	Triple sounds	Jugular pulse	—	106.105 102.101	—	Traumatic pericarditis
37	Scouring and lassitude	1 month	Lethargy ataxia	Profuse scour	+	Venous engorgement	+	—	—	120·90	Subdued 2nd sound Systolic murmur	Mammary and jugular pulse	+	101.101		Endocarditis
38	Blindness	7 weeks	Joint ill recumbency		—		+	+	—	120	—	—		102.102	—	Joint ill
39	Anorexia	2 weeks	—	Melaena	—	Pallor	+	—	+	76·96 88·92	Systolic murmur	General venous engorgement. Mammary and jugular pulse	+	104 101.103 101.102	—	Pneumothorax Endocarditis
40	Retained afterbirth Metritis	8 months	Stiffness Lameness	Anorexia	+	—	—	—	—	—	—	—	—	104	—	?

should be considered as first signs. Moreover some features that are common to the later stages and characteristic of well-developed heart disease were sometimes presented as the first signs. Contingent with this, therefore, was the variable recorded duration of illness.

In those few cases presented with antecedent history of some septic condition such as metritis or septic joints, if the time of appearance of these conditions is accepted as indicative of onset, the duration of the disease was of several months.

However, in the majority the onset was sudden, with anorexia, gastro-intestinal upset, jaundice, respiratory distress, stiffness, or even recumbency recorded as first symptoms. Physical examination revealed possibly a fever, increased heart rate with or without the detection of abnormal heart sounds. In these cases the duration of clinical illness was usually a matter of weeks.

Course of the Disease

Generally speaking the symptoms first noticed became progressively more severe. For example, the stiffness became more crippling, the scour often became intense with occasionally melaena, a markedly rapid loss in condition was very common, and signs of cardiac embarrassment such as venous engorgement, jugular and even mammary vein pulsation with eventually widespread oedema, dyspnoea, weakness, and recumbency was the usual course.

Fever fluctuating between 103° and 107° F. occurred in most cases, but in others the temperature remained normal throughout.

Pulse rates again tended to fluctuate and the slightest exertion frequently caused such pronounced increase in rate as to render its appreciation impossible. Occasionally the pulse was irregular and comparison of pulse rate with heart rates signified a "pulse deficit," *i.e.* the pulse rate was less than the heart rate resulting probably from ventricular extrasystoles.

Heart Sounds

The detection of a murmur is considered a highly significant feature of valvular disease and in man it is reputed to be present in 99 per cent. of cases of subacute bacterial endocarditis. Moreover since the disease commonly affects the mitral valve the murmur is generally systolic. However, it is interesting to note in the rare instances of pulmonary valve affection that the murmur is frequently absent (Seabury, 1947), and Barker (1949), in his review of 36 cases of right-sided bacterial endocarditis, comments on the absence of murmur in 4 cases.

From my own experience and from discussions with other veterinary surgeons who attended some of the cases, it is considered that the detection of murmurs in cattle is not easy and I feel hesitant in stating categorically that they were absent in a number of cases. However, this absence could be real and due to the frequent right-side location of the lesions, or else the advanced insufficiency that could accrue from gross lesions widening the orifice so much that the back pressure of blood is reduced beyond that required to cause a murmur.

However, some abnormalities of heart sounds were detected and include:—

(a) Equal intensity of both heart sounds.
(b) Duplication of 1 or other heart sound.
(c) Prolongation and muffling of the second sound.
(d) Systolic murmurs.

Although no pericardial friction sounds were recognised, it is considered important to point out their possible encounter because of the *post-mortem* finding of pericarditis in some carcases. Similarly, fluid noises may be present.

Pain

John (1947) was particularly impressed by the general severe pain observed in his series of endocarditis cases, and confessed to an inability to ascribe any precise cause.

Pain, observed as a depression, grunting, or abnormal posture, or else resultant from manipulation over the withers, xiphisternum, and the left cardiac area was encountered in 7 of the cases described here. Generally it was of 12 to 48 hours' duration and intermittent, suggestive clinically of superimposed resolvable complications.

The most probable explanation that occurs to me is that they exemplified episodes of gross infarctions of internal organs. Infarctions of the kidneys, lungs, or myocardium were present in over a quarter of the carcases examined.

Haematology

It is generally accepted that examination of the blood picture is useful in the diagnosis of bacterial endocarditis in man. The blood changes encountered vary according to the acuteness of the disease. In the more fulminating type caused by organisms such as staphylococcus and pneumococcus a leucocytosis is usual and if the disease persists there develops a severe anaemia (Whitby & Britten, 1950). The leucocyte picture is, however, variable in the subacute form and though there exists a tendency for the total counts to stay within normal limits, or a little above, a high leucocytosis usually with neutrophilia readily arises on the occurrence of infarction, thrombosis, or other complication. Moreover, a great increase in the number of monocytes and the presence of many macrophages in the blood, particularly in samples collected from the peripheral circulation such as in the ear, are strongly suggestive, though not pathognomonic, of endocarditis. A slight anaemia appearing early and often becoming progressive is almost a constant feature but only rarely does it assume a really severe degree. In type it is usually normochromic normocytic or hypochromic normocytic as is usually seen in chronic infections (Pepper, 1927).

A total of 14 samples of blood collected from 9 confirmed cases of bacterial endocarditis in cattle were examined and the following remarks cover the salient findings.

Erythrocyte Picture

It is apparent from the analysis of the results (Tables IX and X) that there existed a general tendency towards low values for both red-cell counts and haemoglobin concentration though, individually, only a few fell below the normal values given by Holman (1955).

TABLE IX

Red Cell Count (×10 6/c.mm).	Number of samples
Over 6·0	1
5·5 – 6·0	3
5·0 – 5·5	2
4·5 – 5·0	6
5·0 – 4·5	0
Below 4·0	2

TABLE X

Haemoglobin concentration (g/100 ml).	Number of samples
Over 11·0	0
10·0 – 11·0	2
9·0 – 10·0	2
8·0 – 9·0	7
7·0 – 8·0	2
6·0 – 7·0	1

In only 1 case was there any definite evidence of hypochromia as judged from the calculated index of mean corpuscular haemoglobin concentration and though it is difficult to assess changes in red-cell size in cattle blood there was no evidence of macrocytosis. The conclusion derived therefore is that a mild normochromic normocytic anaemia is a feature of the condition in cattle.

The Leucocyte Picture

No marked leucocytosis was apparent in the majority of the samples and in 2 instances only were the total white-cell counts above the 13,000 per c.mm. considered by Holman to indicate leucocytosis. However, neutrophil counts above 5,000 per c.mm. were present in 6 samples and these were accompanied by moderate shift to the left. Though 3 animals showed high monocyte counts, in 1 case only could this be considered a definite monocytosis.

Comments

It is appropriate at this point to compare these blood changes with those found in other conditions bearing some clinical resemblance to endocarditis. In traumatic reticulitis the leucocyte counts are not generally markedly raised but there is a more pronounced shift to the left.

Traumatic pericarditis is more likely to be confused with endocarditis, but generally there is here, a high leucocyte count together with pronounced shift to the left. However, since this is not invariable and the finding in 2 cows with endocarditis of leucocyte counts over 14,000 and 19,000 c.mm. indicates that haematological examination on its own, though valuable, is not infallible as a means for their differentiation, and repeated sampling coinciding with thorough clinical examinations for evidence of infarctions and other crises, is advisable.

Blood Cultures

The importance of blood culture as an aid to diagnosis of a number of infective conditions of man is well recognised and its value is probably greatest in the diagnosis, prognostication, and the initiation and control of treatment of bacterial endocarditis. This is especially so to-day when antibiotic therapy has almost revolutionised the prognosis in cases of subacute bacterial endocarditis (Butler, 1937; Kerr, 1955).

The technique of blood culturing is not difficult and, provided reasonable precautions are taken, very few contaminated samples accrue.

In 8 cases of this series opportunity arose for attempting such cultures. These proved successful in 5 cases in that the cultures yielded organisms similar to those subsequently isolated from the endocardial vegetations. In 3 they were negative in each case on 2 occasions. Possible explanations for the negative results include the fact that not sufficient numbers of cultures were performed to pick up the organism and possibly since the gross lesions involved the right heart that the lungs acted as filters preventing sustained bacteraemia. However, this latter hypothesis is modified by the frequency with which in cattle the left side of the heart is the seat of small lesions presumably arising by spread of organisms *via* the lungs from the gross lesions on the right side. The answer is probably that more numerous attempts should be made during the course of the disease. Indeed it has been strongly emphasised that the larger the number of repeated cultures from the same case, greater is the reliance that can be placed on the results (Butler, 1937).

Diagnosis

It is to be expected that in a disease with such varied manifestations that diagnosis often proves difficult, particularly early in its course. It has no individual feature that can be considered as pathognomonic but the combination of symptoms and signs such as an abnormality of the heart's action; fever—though not constant; evidence of embolic manifestations such as pain, stiffness, or lameness; dyspnoea; and symptoms of digestive upset, should lead one to suspect endocarditis. If valvular murmurs are heard and/or the laboratory examinations indicate bacteraemia, anaemia with little leucocyte changes, haematuria, and proteinuria the diagnosis of endocarditis becomes firmer.

The later features of cardiac failure such as oedema or jaundice may be so marked that if first seen at that stage differentiation further than a diagnosis of cardiac disease may be very difficult and probably unnecessary since it would then be too late to institute therapy.

The failure to appreciate the varied symptoms and signs as manifestation of endocarditis rather than as

primary features, was undoubtedly the main cause for the erroneous diagnosis in some cases of this series. These included traumatic pericarditis and reticulitis, pneumonia, liver-disease, rheumatism, and even dislocation of the hip in 1 cow that was recumbent when first seen. Hypothetically, other conditions that could be confused with endocarditis include nephritis, abscessation of internal organs, septicaemia, mediastinal neoplasia, condtions causing recumbency such as milk fever, and other abnormalities of the heart, *e.g.*, myocarditis, congenital defects, or those malactions resultant from anaemia or impediment to the circulation such as fibrosis of the lung.

Ideally the first step towards diagnosis is the determination of the presence of cardiac disease and subsequently assessing whether this is primary or directly secondary to some other conditions. From the aspect of differential diagnosis certain conditions may be eliminated through their expression of distinctive signs, *e.g.* the reticular grunt, considered by Williams (1955) as pathognomonic for traumatic reticulitis.

Differentiation of the cardiac disease is likely to prove the more difficult, and of these the most difficult and important would be from traumatic pericarditis. It will be remembered that a number of the endocarditis cases described showed a secondary pericarditis and later in the course excess transudate was frequently present in the pericardium. Auscultation in these cases may therefore have revealed friction and/or fluid sounds with muffling of the heart sounds similar to those present in tramatic pericarditis.

It is apparent therefore that a careful appraisal of many features is necessary before establishing a diagnosis.

Treatment

From the very limited information available on this aspect little constructive opinion can be offered. Sulphapyridine and penicillin therapy was tried in a few cases but the animals succumbed though, during the course of treatment, high temperatures frequently came back to normal. Nevertheless Brown (1955) reported the successful treatment of 2 suspected cases of endocarditis.

Two features of treatment, however, merit comment. Firstly the success of therapy is obviously dependent upon the sentitivity of the causative agent to the particular drug used. The enterococcus is notoriously resistant to both bactericidal and bacteriostatic agents and according to *in vitro* tablet sensitivity tests performed on the 16 strains isolated from this series they were all resistant to Streptomycin, Terramycin, Chloramphenicol, Penicillin, Tetracycline, and Aureomycin. An omission in the tests was that the strains were not exposed simultaneously to streptomycin and penicillin since success is reported following the use of both substances together in human cases of enterococcal endocarditis (Cates, Christie & Garrod, 1951).

The second feature concerns the time at which the therapy is started. Early institution is essential for success, for once evidence of congestive cardiac failure is manifest then poor results are frequent (Newman, Torres & Guck, 1954).

Conclusions

Bacterial endocarditis more so than most other cardiac diseases of cattle presents several problematical, although interesting, features. Because of the multiplicity of organs and systems that is involved, the disease provides an excellent exercise in the correlation and assessment of symptoms and signs necessary for its diagnosis.

Little is known about the early features of the condition and, because these would be difficult to ascertain in naturally occurring cases, it is probable that detailed observations on experimentally reproduced cases would provide the best approach to their elucidation.

Many of its features parallel those reported for bacterial endocarditis of man. The clinical manifestations, numerous pathological findings, and the low-grade virulence of the causative organisms encountered in the majority of cases are distinctively similar to those found in the human subacute variety. However, there are differences of which the most serious is the valvular distribution of lesions.

Summary

Several aspects of bacterial endocarditis of cattle are recorded and described. It contributed materially to the causation of martality of cattle in South-West Wales, having a proportional death rate of 3.93 per cent. and an estimated annual crude mortality rate of 5.2 per 10,000 head at risk. A marked discrepancy between estimates of mortality and morbidity rates revealed in a survey is considered to have arisen mainly from non-recogition of the disease as such during life.

From the *post-martem* examination of 28 carcases it was appreciated that the findings could be considered under 2 broad classifications: those accruing from an embolic phenomenon, *e.g.* infarctions of various organs, focal embolic nephritis, and embolic abscesses; and the other manifestations such as brown induration of the lungs, nutmeg liver accompanied occasionally by fibrosis and jaundice, oedema, and excessive transudation into the body cavities, resulted from terminal cardiac failure. It is difficult to offer a precise status for the ulcerative, non-purulent, arthritis.

The cardiac lesions were exuberant, typically cauliflower in appearance, and were widespread in distribution on both valvular and parietal endocardium. The tricuspid was the commonest seat of affection either alone or in association with other sites.

In a few cases with antecedent clinical histories of some septic conditions such as metritis and septic joints, pyogenic bacteria like *C. pyogenes* and staphylococci were incriminated as causative, but from the majority an α- or non-haemolytic streptococcus was isolated and the 16 strains of these that were fully examined proved to be enterocci. The mode of infection in these cases was not apparent though circumstantial evidence suggests the possible implication of the liver fluke.

The autopsy findings offer explanations for the varied clinical manifestations recorded in 21 cases,

and from the consideration of both aspects in the investigation a reasonable working approach to diagnosis is deduced. This is dependent upon careful assessment of symptoms and signs combined with laboratory examinations such as blood culture, haematology, and urinanalysis.

Only in those cases recognised early in the course of the disease is therapy likely to prove successful.

Many aspects simulate bacterial endocarditis of man, but others, notably the distribution of vegetations, provide contrasting features.

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Veterinary surgeons practising in the area, too numerous for individual mention here, deserve my sincerest thanks for their collaboration; special acknowledgment is made to 2 of them, *viz.* Messrs. F. V. John, Llandilo, and E. I. Williams, St. Clears, since being themselves keenly interested in the problem they contributed the most.

Thanks are also offered to Mr. R. I. Isaac, B.SC., Aberystwyth, Miss M. Moore and Mr. P. Brown at Cambridge, for their technical assistance and finally, but not least to the knackery owners and slaughtermen in South-West Wales for their keen co-operation.

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THE SPEAKER'S INTRODUCTION

Mr. E. T. Rees Evans, in introducing his paper, said that the opening remarks made by Osler when presenting the Gulstonian Lecture of 1885 on Malignant Endocarditis appeared to be most pertinent, and it might be of interest to quote them:—

"It is of use from time to time to take stock, so to speak, of our knowledge of a particular disease, to see exactly where we stand in regard to it, to inquire to what conclusions the accumulated facts seem to point, and to ascertain in what direction we may look for fruitful investigation in the future. With your permission, Sir, I propose to do this in a case of that most interesting disease generally known as ulcerative endocarditis . . ."

The Congress, being held at Cambridge in 1957, was most appropriate for the consideration of a disease afflicting the heart since the year was the tercentenary of the death of William Harvey who in his book *De mortu cordis* first presented evidence for the circulatory movement of the blood—a discovery generally considered to be the greatest in medical science and undoubtedly one which contributed as much to veterinary science. Cambridge could claim a close association with that great man, for he studied at Caius College for 6 years.

There was little he (Mr. Rees Evans) desired to add to the paper, but inadvertently he had omitted from the final draft reference to the possible value of techniques such as electrocardiography, radiography, phenocardiography, and recording of blood pressures, as ancillary aids in diagnosis. Whereas they were obviously procedures not freely available to veterinary surgeons in practice, it was believed that developments in their application in

veterinary medicine should eventually prove valuable both as detectors of abnormalities in themselves, but also as means of training the senses to a better degree of perceptiveness.

The opportunity occurred during the year for applying those methods in the study of a case of endocarditis in a 9-year-old Jersey cow, and Mr. Littlewort, who was responsible for those examinations, had signified his willingness to contribute the relevant results to the discussion.

Vacirca and Ragini (1952-3) reported on their electrocardiographic findings in one case and concluded that the changes noted, which indicated a simple block, were not specific for the condition. That apparently was the position in the human field wherein it was generally accepted that electrocardiography was mainly of help in diagnosing the underlying heart disease upon which the endocarditis was superimposed. However, a fairly characteristic electrocardiogram, rather similar to cardiac infarction, was reported to be found in gross pulmonary embolism, and therefore electrocardiography could possibly prove valuable in studying some of the complications of endocarditis in cattle.

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The following contribution by **Dr. S. D. Elliott** was read in his absence by Professor Beveridge:—

Streptococci isolated at autopsy by the author from the blood or heart valves of 16 cases of bovine endocarditis had been examined serologically. All were found to belong to Lancefield's group D and all to one or other of 2 distinct serological types provisionally designated type D10 and type D15 respectively. In 8 cases type D10 was isolated and in 6, type D15, while in 2, a mixed infection was present, both types being isolated from each (Table I).

In an attempt to gain information concerning the incidence of types D10 and D15 in other situations, a serological survey had been made of group D streptococci isolated from cows (milk, rectum, and vagina), and from human cases of subacute bacterial endocarditis (blood culture). Table II showed the incidence of group D streptococci types D10 and D15 in apparently normal milk from cows in the same geographical area as that in which the cases of bovine endocarditis occurred. All the milk streptococci examined were isolated by Mr. L. E. Hughes, veterinary investigation officer, Aberystwyth. Mastitis had been a problem in all the herds examined, but the pathological significance of the streptococci isolated from the milk was doubtful. It would be seen that the bovine endocarditis types were fairly common in milk from that

TABLE I

SEROLOGICAL TYPES OF GROUP D STREPTOCOCCI ISOLATED FROM 16 CASES OF BOVINE ENDOCARDITIS

Number of cases yielding Group D streptococci*	Number of cases yielding Group D streptococci of stated type		
	Type D10	Type D15	Mixed infection Type D10 + Type D15
16	8	6	2

* *Post-mortem* cultures from heart blood or vegetations.

area, and that single types tended to predominate in particular herds. It had not proved possible to identify either type D10 or D15 amongst streptococci from rectal and vaginal swabs from 8 cows belonging to the Cambridge Veterinary School herd.

Group D streptococci were the cause of subacute bacterial endocarditis in about 10 per cent. of human cases. Such cases were of particular interest in that they were usually resistant to treatment with penicillin. Among 36 strains of group D streptococci isolated by blood cultures from patients with that disease, type D10 had been encountered once and type D15 three times.

The type-specific antigens of group D streptococci were probably polysaccharides and in most strains they were liberated from the bacterial cells by proteolytic digestion. During the early stages of tryptic digestion of formalin-killed streptococci, the type specific polysaccharides might be found in the supernate relatively free from other bacterial antigens, and might then be identified by precipitin reactions with hyperimmune rabbit sera prepared with streptococci of homologous type. Precipitin reactions between antigen extracts prepared in that way and crude rabbit anti-sera were usually specific, but could be confirmed using antisera from which non-type specific precipitins had been removed by absorption with group D streptococci of heterologous type. A more detailed description of that method would be published at a later date.

The Opener

Mr. P. J. N. Pinsent said: "I consider it a great privilege to be given the opportunity to open the discussion on Mr. Evans's paper, and my first and very pleasant duty is to congratulate him on an excellent and most interesting piece of work.

"I can make no claim to authoritative knowledge of bovine endocarditis, but together with colleagues at the Liverpool School I have been able to make daily observations upon several cases of the disease throughout the greater part, if not all, of its course, and I would like, to-day, to consider briefly certain aspects of the clinical picture in relation to diagnosis.

TABLE II

SEROLOGICAL "TYPES" OF GROUP D STREPTOCOCCI ISOLATED FROM MILK SAMPLES FROM 37 COWS IN 8 HERDS

Herd identification	Number of cows examined	Number of milk samples yielding Group D streptococci	Number of cows yielding Group D streptococci of stated type				
			Type D10	Type D15	Type D76*	Type H69D5*	Type unidentified
38/57	4	4	—	3	—	—	1
39/57	3	8	—	3	—	—	—
109/57	1	1	—	—	1	—	—
213/57	18	21	(12)	—	—	—	6
220/57	1	1	—	—	—	—	1
248/57	6	6	(2)	(1)	—	(1)	2
285/57	2	2	—	—	—	—	2
288/57	2	3	—	1	—	—	1
Total	37	46	(14)	7 (1)	1	(1)	13

* Group D "types" established by Dr. R. C. Lancefield to whom I am indebted for "type" strains and antisera.
( ) Indicates strains whose identity has not yet been confirmed by precipitin reactions with absorbed antisera.

Onset

" The first point I wish to make is that I believe the onset to be basically insidious, producing clinical signs which are very slight at first, consisting only of slow loss of condition with diminution of appetite, but gradually becoming more marked, sometimes over a course of many weeks, until signs of heart failure with circulatory interference appear as a terminal phase in the last days before death. Undoubtedly cases are presented apparently of sudden onset, but I think there are two reasons for this. Firstly, the lesion which acted as the primary focus, for example septic arthritis, or abdominal abscessation following traumatic reticulitis, may itself produce symptoms of such severity and rapidity of onset that the clinical picture produced completely masks the signs of slowly developing endocarditis until a late stage. Secondly, it seems quite possible for endocarditis to develop insidiously from a minor and probably transient primary focus, and to remain unnoticed until severe complications such as extensive infarction of a lung, or the interesting lameness described by Mr. Evans, develops, giving the impression of sudden onset. In such cases it is very easy for the clinician to treat the primary focus, or the complication, as the case may be, believing it to be the sole cause of ill-health.

" Once signs of heart failure such as distension of jugular and mammary veins or filling of the legs have occurred, diagnosis is simplified to the extent that it becomes reasonably obvious that the disease process directly involves the heart; but if diagnosis is to have any practical value it must surely be made early, at a stage when treatment might possibly be expected to have satisfactory results, or alternatively when changes due to embolism and infarction are at their minimum and slaughter for salvage might reasonably be successful. The early clinical signs are, therefore, of great importance.

Early Clinical Picture

" The animal's bodily condition deteriorates progressively throughout the course of the disease. Even in cases of apparent sudden onset the animal may be thin when first seen, which is perhaps evidence in favour of insidious onset. We have, however, been impressed by the fact that appetite, though far from normal, is by no means absent, and that rumination may be observed until a late stage in the disease, though not with normal frequency or vigour. Demeanour, also, except in cases where a painful or toxaemic primary focus is still in existence or a painful complication exists may remain relatively bright, and even in the terminal phases there is not the great depression associated with traumatic pericarditis. Milk yield is lowered, but may be by no means absent, one case giving 30 lb. daily until the terminal phases.

" There is a tendency for appetite, rumination, demeanour, and milk yield to deteriorate gradually throughout the course of the disease, with transient and variable improvement during periods of antibiotic treatment until the terminal phase of heart failure leads to rapid deterioration and death.

" None of our cases showed significant diarrhoea, nor was there any haematuria, although 2 out of 3 cases examined showed albuminurea. In the one positive case of 3 subjected to blood culture, it may be of interest that the causal organism, haemolytic *Staphylococcus aureus*, was also cultured from the urine. Anaemic changes were never more than marginal.

Pain

" Pain has not been a marked feature until the terminal stages, except where a painful primary focus such as traumatic reticulitis or septic arthritis was still in existence, or where the interesting secondary lameness already described was present. In other cases pain was absent, or was manifested by periods of rigidity of stance, with abduction of left or both elbows, and discomfort when pressure was applied to the left ventral aspect of the chest, all signs which may well lead to an erroneous diagnosis of traumatic reticulitis, but which I agree with Mr. Evans are probably indicative of infarction within the chest.

Respiratory Rate

" Respiratory pattern seems to be of considerable clinical importance. Respirations are usually noticeably accelerated and may even be somewhat laboured and blowing in character. As the disease progresses this abnormal respiratory picture becomes progressively more marked, and very slight exercise may produce severe dyspnoea with outbursts of coughing. I think that these respiratory symptoms are quite useful diagnostically in conjunction with the other signs, but they may well lead to an erroneous diagnosis of pneumonia when the animal is first examined, particularly when one remembers that pathological changes in the lungs due to infarction may well be present. This accelerated respiratory rate appears to show little change during periods of antibiotic treatment.

Temperature and Pulse Rate

" We have already discussed briefly the effect of treatment on appetite, rumination, and demeanour, and its lack of effect upon respiratory rate, but it is perhaps of most interest in relation to temperature and pulse rate. Temperature in our limited series has been between 104° and 106° F. on first examination, with a definite tendency to remain high throughout. Pulse rate is usually high, tending to rise as the disease progresses, and in several cases has been 100 or above throughout. One expects that treatment of a case of pyrexia with suitable antibiotics will produce a proportionate fall in both temperature and pulse, but in this disease such treatment produces a spectacular effect upon temperature, which may fall from 105° to normal in 24 hours, rising again as soon as treatment is discontinued, whilst the effect upon pulse rate is slight or completely absent. I doubt very much whether this peculiarity is pathognomic of endocarditis, but it is at least useful additional evidence.

White Cell Picture

" The effect of antibiotic treatment on the white cell picture is also of interest. Our cases have shown a leucocytosis and neutrophilia varying from comparatively slight increases up to total counts as high as 26,700 per cu. mm., with the percentage of total neutrophils as high as 66.5 per cent. White cell counts are thus of comparatively little value in differential diagnosis as pictures similar to those of both traumatic reticulitis and traumatic pericarditis may be obtained. The white cell count may even be in normal range, particularly if antibiotic treatment is being applied, the effect of such treatment being to lower the total white cell count, and neutrophil percentage with a corresponding increase in the lymphocyte percentage. This effect is reversed when treatment is withheld.

Heart Sounds

" I have left discussion of heart sounds until this point as they have caused considerable perplexity. They do tend to be very loud and pounding in nature, audible at times over any part of the thoracic and abdominal walls, and in one case a pulse deficit was present, but I must admit that in one only of 6 cases subjected to careful auscultation could any sounds indicative of cardiac incompetence be heard, and even in this case the sound, a systolic murmur, was heard only in the last 3 days of life when venous distension was already well marked.

" Other clinicians have found similar difficulty and Mr. Evans has suggested reasons for it. Our findings tend to support him, as the endocardial lesion in the positive case was of the mitral valve, whereas in 4 out of the other 5 cases either the only lesion, or the major lesion, was in the right side of the heart. The fifth case did admittedly show a left-sided lesion, but it was comparatively small, and affected the ventricular wall much more than the valve.

" Medical opinion in the human field seems to be that a diagnosis of endocarditis is untenable in the absence of abnormal cardiac sounds, and I feel that one is not justified in making a firm diagnosis of endocarditis in the bovine subject, however suggestive the clinical picture and laboratory findings may be, unless abnormal cardiac sounds can be heard. Even when venous engorgement is apparent I believe this criterion holds, because although traumatic pericarditis may be differentiated at times by the great

depression, the signs of toxaemia, the muffled heart sounds, and the complete lack of response to treatment, other cardiac lesions do occur in cattle from time to time which may cause confusion. For example I have twice met cases of myocardial abscessation in cattle, without any endocardial lesion, which produced a clinical picture closely resembling that of endocarditis.

Treatment

" This difficulty obviously affects evaluation of treatment. It seems likely that treatment is hopeless once definite clinical signs of venous congestion indicative of heart failure are present, particularly when one remembers that in the bovine animal treatment is useless unless full productivity is restored; but although I feel that at least one early case has responded completely to massive penicillin therapy, one cannot claim success in the absence of confirmation of diagnosis. A pounding heart, or even a pulse deficit are not in themselves pathognomic of endocarditis; and if Mr. Evans is correct, the preponderance of right-sided lesions will tend to make definite confirmation by cardiac auscultation almost impossible in most early cases.

" All I can say, regarding treatment, is that in our small series of cases confirmed by *post-mortem*, it has been ineffective, the nearest we have come to success being in one case where massive penicillin therapy for 6 days produced apparent clinical recovery which lasted for 3 weeks before relapse occurred.

" Treatment has consisted of large doses of penicillin and streptomycin, both separately and combined, for periods of from 2 to 10 days. We have also used sulphadimidine in one case. There has not yet been opportunity to use the higher antibiotics, but as Mr. Evans has pointed out, their success as compared to penicillin will depend upon the organism concerned.

" In conclusion I would like, once again, to thank Mr. Evans for his paper. I feel sure that you have all found it as interesting and stimulating as I have done."

Mr. Pinsent concluded by showing two slides. The first illustrated the effect of treatment upon the white cell picture.

The second slide showed the effect of treatment by antibiotics upon temperature and pulse.

The General Discussion

Mr. Eric I. Williams (St. Clears) said: " I would also like to congratulate Mr. Rees Evans on his excellent paper which is all the more meritorious when one realises that it was written under the strain of a severe illness.

" During the past 10 years I have encountered 12 cases of endocarditis, only one of which recovered—as a bad doer. There was no age incidence and most cases followed a history of metritis, etc. However, one would be unwise to dogmatise that endocarditis is a subsidiary condition.

" I would agree that this is a very difficult ailment to recognise in practice, and that no symptoms may be accepted as being pathognomic. However, in my cases two factors have led me to suspect endocarditis, *viz.* accelerated pulse, 100 to 120 per minute at rest, associated with lameness or stiffness of one or more limbs. A characteristic feature is that this lameness is not confined to the same limb if the animal is examined on successive days.

" Mr. Rees Evans's contribution pinpoints two clinical factors:—

" (a) Whilst our aim is always to cure ailments, there is, after all, a true fascination and satisfaction in arriving at a correct diagnosis, even if the animal succumbs.

" (b) Endocarditis is yet another condition which provides a rude reminder of our lack of ability to interpret normal physiological sounds. The previous speakers have all stated how difficult it is to detect any abnormal heart sounds even in advanced cases. I agree entirely with these observations and I attribute my own failures to my lack of ability and experience in interpreting normal heart sounds. (It is significant that in the series of 12 cases, the one animal which showed obvious systolic murmurs was the only one to recover.)

" It occurred to me when reading this paper earlier to-day that an investment in a tape-recorder might be a good idea. Whereas the cows may not be taken home with us, at least a recording of normal heart sounds of a herd of milch cows may well be enjoyed in a cosy armchair on a winter's evening, and much could be learnt in this way. One would then be more competent to detect abnormal heart sounds. I understand that this instrument has been used to good effect in identifying the borborygmal sounds in cases of displacement of the abomasum."

Mr. C. G. Littlewort (Cambridge): " In his very exhaustive review of bacterial endocarditis in cattle Mr. Rees Evans has told us how he and other authors have described, among other signs and complications of the condition:—

1. Pulsation of the jugular veins and of the supramammary veins.
2. Cardiac murmurs.
3. ' Duplication ' of one or other of the heart sounds.
4. Ventricular extrasystole, or premature beat.
5. Right ventricular hypertrophy.

In one of the cases included in the series described (that of a 9-year-old Jersey cow), I had the opportunity to make certain physiological recordings which appear to confirm some of these findings and throw fresh light on others. Mr. Rees Evans has, therefore, asked me to show you slides made from those recordings.

The first three relate to:

Venous Pulsation

Pressure changes in the jugular vein were recorded by means of a catheter passed through a large-bore hypodermic needle. A simultaneous recording of Lead II E.C.G. provides a standard from which to judge the timing of events in the cardiac cycle.

A similar, but indirect capsule recording was made from the supramammary vein. Both demonstrate the pulsation of the vessels. The abnormally high, somewhat premature " v-wave " of the phlebogram indicates the presence of tricuspid incompetence, and shows that, in this case at least, its effects predominate over those of stenosis.

Murmurs, and ' Duplication ' of the Heart Sounds

Phonocardiographic records demonstrate the presence of a systolic murmur, even though the lesion was of the right A-V valve, and also of triple, or ' gallop ' rhythm. The latter resulted from an abnormal auricular, or 4th sound preceding the 1st sound, rather than from true ' duplication ' or ' splitting ' of the normal 1st sound.

Extrasystole, and Right Ventricular Hypertrophy

Isolated extrasystoles commensurate with an abnormally irritable myocardium are shown in the electrocardiogram.

This record also suggests the presence of right ventricular hypertrophy, thus providing *ante-mortem* evidence of the tricuspid lesion. Such a finding might, in the later stages of the disease, help to distinguish bacterial endocarditis from pericarditis in which such unilateral hypertrophy would be unlikely. A similar E.C.G. pattern has been reported, though not, I think, interpreted, in one other case of bacterial endocarditis by Vacirca and Ragini in Italy in 1953."

Reference

VACIRCA, G., & RAGINI, M. (1952-3). *Ann. Fac. Med. Vet. Torino.* **3.** 188-99.

The Reply

Mr. Rees Evans, in reply, recalled that in his opening remarks he quoted Osler, and one pertinent part of that quotation included the words " to ascertain in what direction we may look for fruitful investigation in the future." It brought out the point that the application of physiological recordings and such things would train the senses of investigators—hands, eyes, and nose—for the better perception of variation in pulse, sounds, and so on.

Mr. Pinsent referred to the fluctuations which occurred when antibiotic therapy was undertaken. The author wondered whether that could not be the reflection of the antibiotics as a bacteriocidal agent cutting down infarction

as a result of which there would be no soft friable emboli.

As to the question of onset, he felt that with further investigation it would be possible to answer that point. In his view the organisms causing the condition could be classified into two main types. There were the Enterococci which were relatively non-pyrogenic, and in those cases onset would probably be insidious. In the case of the Staphylococcus, they were far from pyrogenic and onset would be more pronounced.

The question of lameness was intriguing. The *post-mortem* appearance was quite interesting as was the type of lesion which was seen as an ulceration of the cartilage.

A Mucosal Disease of Cattle

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Introduction

ONE of the main objects of this paper is to draw attention to a condition first recognised in this country a few years ago and which in its mildest form at least may be considerably more widespread than is believed.

The difficulty in carrying out large-scale research on a disease of this nature, where the calf is the only available experimental animal, will be appreciated. Nevertheless, it is hoped that the information provided by the work carried out to date will stimulate a wider interest in this condition and so add to our knowledge of it particularly in regard to its epidemiology.

The clinical features of the disease varied from herd to herd and could broadly be classified under the headings: mild, severe acute, and chronic. The condition has occurred in several breeds maintained under widely varying conditions of management and at all seasons of the year. Changes in the tissues were confined to the mucosa of the alimentary tract.

The disease had many features in common with the conditions described in North America under the heading Mucosal Disease.

There were notable differences between the naturally occurring and artificially induced disease and for this reason it is desirable to describe these forms separately.

The Natural Disease

Outbreaks investigated have varied from a mild transient illness to a severe haemorrhagic gastro-enteritis. Chronic forms mainly involving adult cattle have been encountered. Table I summarises the outbreaks investigated.

Mild Outbreaks

These were characterised by subclinical or transient upsets in an affected herd. Examination of apparently normal animals in contact with a clinical case showed that some had high temperatures and ulceration of the mouths. Clinically, the symptoms varied from pyrexia with mucoid nasal discharge, followed in some animals by scouring of short duration. Morbidity was high but mortality was low.

A typical mild outbreak occurred in a commercial herd of Herefords, in the County of Herefordshire (Farm 7). One four-month-old calf of a batch of six housed in a box and suckled by three nurse cows, developed severe disease. This animal died after an illness of one week. A few days later another calf in an adjacent box became ill and died after being sick for a few days.

The remaining stock were examined one week after the first death occurred. Of the five contacts to the first case, one had a temperature of 105°F. with ulceration of the buccal mucosa. This animal was eating normally and was otherwise healthy. A second showed enlarged lymph-nodes, with nasal discharge and thickened, dry skin over the neck and shoulders. It had been dressed with tractor oil, to cure ringworm. Another had peridental cyanosis around the bases of the incisor teeth, a fourth calf was scouring. Of the nine calves which were in contact with the second animal to die, eight had temperatures of over 103°F. with lesions in the mouth, varying from hyperaemia to ulceration of the mucous membrane. One had hyperkeratosis of the skin over the neck.

There were a further 31 calves under eight months of age, one of which was salivating and showed hyperaemia of the nares. No abnormalities were observed in a further 79 young cattle of up to two and a half years of age, nor in 18 nurse cows. No further deaths occurred.

Severe Acute Outbreaks

This has been encountered in the Midlands, Kent, Devon, Cambridge and Berkshire. Morbidity was up to 60 per cent. of an affected batch and mortality was very high. Outbreaks have occurred throughout the year in housed and grazing cattle. The symptoms are those which may occur in an occasional severely affected animal in a mild outbreak.

The disease occurred in animals 4 to 18 months of age with no apparent spread to younger or older cattle in close proximity. Pyrexia might occur before or during illness. The onset of disease was characterised by anorexia, dullness and mucoid nasal discharge. Diarrhoea followed by tenesmus with the voiding of blood-stained mucus was evident, and frequent drinking occurred in the early stages. The nasal discharge became thickened and dried to form encrusted debris on the muzzle. The nares and buccal cavity showed lesions varying from hyperaemia to ulceration of the mucous membrane. Intense reddening of the gums around the bases of the incisor teeth could be observed in some. The animals lost condition rapidly. Lameness was not observed although ulceration occurred between the hoofs of cattle in one outbreak. Symptoms referable to nervous involvement have not been noted.

An outbreak typical of the severe acute type occurred in a group of 50 calves 5 to 9 months of age (Farm No. 5). The herd was self-contained and pedigreed, with a total of about 300 head on the farm. Twenty-one calves of the affected batch died. The epidemiology of this outbreak is of interest. During the first week of May, two calves became ill and died three and four days after onset of illness. Coccidiosis was diagnosed after examination of faecal smears. The following week eight calves were affected. At this stage corrosive poisoning was suspected but the availability of a poison could not be shown. Because of the severity and type of the lesions cattle plague was finally suspected. Nine

calves were affected in the third week, and a further two were sick during the fourth week. All of these died or were killed *in extremis*, from 4 to 24 days after onset of illness. The disease appeared to stop abruptly in the fourth week and no new cases were recorded. No spread was noted to younger and older cattle which had indirect contact with the affected batch.

Other severe acute outbreaks have been suspected as malignant catarrh because of enlargement and engorgement of lymph-nodes with perinodal oedema.

Chronic Outbreaks

Characteristically, the chronic form ran a prolonged course of up to several months in a herd and affected mainly adult animals. At frequent intervals different individual animals showed high temperatures and scouring, with loss of milk yield. Ulceration of the oral cavity and poor condition of the animals was frequently observed, together with abortion not attributable to bacterial causes. Ulcers were frequently found between the claws of animals in one herd.

Post-mortem Lesions

These varied from a mild, catarrhal enteritis to a severe, haemorrhagic gastro-enteritis with ulceration of all or parts of the alimentary tract. The ulceration frequently extended into the nares. In severe cases the muzzle was encrusted with dried exudate and debris. The mouth was "dirty" and often yellow caseous material coated the tongue. Ulceration was frequently observed on the lips, buccal mucosa, tongue and hard and soft palates. These lesions sometimes extended into the pharynx and even the larynx. The surfaces of these cavities were coated with yellowish, necrotic debris and the mucosa was intensely inflamed. The oesophagus frequently showed ulceration or raised areas which were darker in colour than the surrounding mucous membrane and which had their long axes in the sagittal plane. The mucosa of the rumen and reticulum was frequently dry-looking and yellowish in appearance. The epithelium was easily removed by rubbing. The contents of the omasum were sometimes found to be very wet, and the mucosa necrotic.

In the lower part of the digestive tract catarrhal enteritis was observed in some, with no other lesions. In severe affections, the whole intestine was intensely inflamed with discrete haemorrhages and ulceration of the mucosa. The abomasum showed rounded raised, light-coloured lesions up to 1 cm. in diameter; these sometimes occurred in the small intestine. In the small intestine, Peyer's patches were frequently intensely reddened and raised above the general level of the surrounding tissue. The mucous membrane was entirely stripped from the duodenum. Characteristically, the lumen of the small intestine was empty of ingesta and contained thick, glairy, tenacious mucus in which clots of blood were found. The intense inflammation of the folds of mucous membrane of the large bowel and rectum gave the appearance of longitudinal striping.

Changes noted in the lymphatic system were marked enlargement of the lymph-nodes with perinodal oedema of the subcutaneous tissue. On section, they appeared very wet and tumefied, and were frequently cherry-red in appearance. The haemolymph nodes were prominent.

Bacteriological Examination

Cultures of the intestines and organs, using aerobic, anaerobic and 10 per cent. CO_2 atmospheres, showed various organisms but none of known pathogenicity.

Experimental

Clinical Findings

Inoculation of experimental calves was carried out using citrated whole blood, lymph-node suspension or lymph-node plus brain suspension injected by intravenous, subcutaneous or intraglandular routes. The disease induced was mild. A positive reaction was characterised by pyrexia occurring 6 to 10 days after inoculation. The temperature rose suddenly to as much as 107.6°F. and fell within 24 hours. Coughing and scouring of short duration was noted in about half the animals which showed a temperature rise. Many calves showed no other symptoms and continued to eat normally. Enlargement of the lymph-nodes sometimes occurred and in a few animals ulceration of the buccal cavity began a few days after the temperature rise and persisted for up to 10 days.

One of two attempts made to transmit the experimentally induced disease by contact failed. Experimental animals placed in contact with natural cases contracted infection and sickened within the incubation time of the experimental disease.

Post-mortem findings in Experimentally Infected Animals

Nine animals were killed; four at the height of the temperature reaction, two at three, one at eight and one at 12 days after the temperature reaction. Few changes were found. Ulceration of the alimentary tract, with the presence of clotted blood and tenacious mucus in the lumen of the intestine, together with congested Peyer's patches was found in two. A further calf killed 88 days after a reaction showed no lesions.

Transmission and Cross Immunity Tests

Transmission experiments in calves were carried out with material from eight of the 10 outbreaks encountered. Details of these outbreaks are contained in Table I.

In order to ascertain the relationship between the various strains isolated, calves inoculated with material from each outbreak were tested against a single strain, the laboratory strain, hereafter recorded as L.S. This strain was isolated from Farm No. 1, the first outbreak investigated.

Cross immunity tests were also carried out in certain instances, by challenging calves previously inoculated with the laboratory strain with strains isolated from outbreaks. This was done with strains

TABLE I

OUTBREAKS INVESTIGATED

Outbreak and period	Owner	Type of stock	Total stock	Affected batch	Mortality	Management and observations	Experimental transmission
1 January to March 1953	Midlands	Pedigreed attested Friesians—closed		50 to 60 calves	8 × 6 months	Housed in tubular steel pens. Young calves in direct contact showed no illness. Course six weeks in herd.	+
2 June 1954	Midlands	Closed pedigreed Ayrshires	127	8	3 × 4 months	Housed. Calves ill about three weeks before death	+
3 May 1955	Midlands	Commercial herd	59 calves	4	2 × 4 to 6 months	Only the affected stock was housed	+
4 October 1955	Kent	Dairy herd		12	2 × 18 months	Grazing. Scouring about one week before death	+
5 February to March 1956	Devon	Closed pedigreed South Devons	280	20 × 14 to 15 months	4	Yarded	+
6 May to June 1956	Kent	Closed pedigreed Ayrshires	about 300	50 × 5 to 9 months	21	Yarded and grazed. Ulceration between claws, no lameness	+
7 October 1956	Hereford	Commercial Herefords	144	16	2	Housed and yarded. Deaths approximately one week apart. Subclinical disease in normal contacts	+
8 October 1956	Cambridge	300 dairy herd and rearing Ayrshires	300	12 10 to 12 months	5	Housed. In November three died within 36 to 48 hours of symptoms of severe diarrhoea and dysentery. Marked thirst, complete anorexia and died quietly	not carried out
9 November 1956	Berkshire	Commercial rearing Cross beef	46	6 yearlings	3	Affected stock bought in, drinking a lot. Pyrexia, ulceration of mouth and between claws. Nasal discharge. Three apparently normal contacts had high temperatures and nasal discharge. 40 others, one of which had n.d.	not carried out
10 September to to March 1956–7	Ayrshire	Commercial rearing	100	18	5 × 1 year 3 × 3 years	50 per cent. of affected stock died. Recovery in survivors about two months	+

isolated from Farms 2, 4, 5, 7 and 10. These strains are recorded in the tables as F2, F4, etc.

To be in a position to assess the results of such experiments however, it was essential to ascertain how calves inoculated with the laboratory strains would react later to a challenge inoculation with the same strain. The results of these inoculations with the laboratory strain are set out in Table II and those of field strain inoculations and cross immunity test in Table III.

It will be observed from Table II that five of the calves which reacted to the laboratory strain, reacted a second time when challenged later with the same strain. Similarly, it will be noted in Table III, that four of the calves which reacted to inoculation with field material from various sources (F4, F5 and F7) also reacted a second time when challenged with the laboratory strain. Table III also shows, as would be expected from the results shown in Table II, that two of the calves which reacted to the laboratory

TABLE II

SUMMARY OF RESULTS OF CALVES INOCULATED WITH THE LABORATORY STRAIN

Primary inoculation		Challenge inoculation		Interval between inoculations				Number not challenged
Number of calves	Reaction	Number of calves	Reaction	2 to 4 weeks	1 to 2 months	2 to 4 months	Over 4 months	
105	+	5	+	1	2	2		69
		31	—	10	3	15	1 at 8 1 at 13 1 at 22 months	
19	—	6	+	2	3	1		5
		8	—	4		2	2 at 7 months	
124		50		17	8	20	5	74

TABLE III

DETAILS OF INOCULATIONS WITH FIELD STRAINS AND CROSS IMMUNITY TESTS WITH THE LABORATORY STRAIN

Origin of field inoculum	Primary inoculation				Interval before challenge	Challenge inoculated			Remarks
	Strain	Number inoculated	Reaction +	Reaction —		Strain	Reaction +	Reaction —	
Farm 2	F2	2	2		1 to 2 months	L.S.		2	These calves had a further inoculation with L.S. and no reaction was observed
	L.S.	3	3		2 to 4 weeks	F2	1•	2	
	L.S.	1		1	2 to 4 weeks	F2		1	
Farm 3	F3	2	2		2 to 4 weeks	L.S.		2	
Farm 4	F4	3	3		2 to 4 weeks	L.S.	2•	1	Further inoculation of 1+ and 1— with L.S. No reaction. Further inoculation with L.S. No reaction.
	L.S.	1	1		2 to 4 weeks	F4	1		
	L.S.	2	2		2 to 4 months	F4		2	
Farm 5	F5	4	4		2 to 4 weeks	L.S.		4	
	F5	2	2		1 to 2 months	L.S.	1	1	
	L.S.	2	2		4 to 6 months	F5		2	
Farm 6	F6	3	3		2 to 4 weeks	L.S.		3	
Farm 7	F7	2	2		2 to 4 weeks	L.S.	1	1	
	L.S.	2	2		2 to 4 weeks	F7		2	
Farm 10	F10	2	2		Not yet challenged				
	L.S.	1	1		1 to 2 months	L.S.		1	1 to 2 months later challenged F10 — negative.
	F7	1	1		2 to 4 weeks	L.S.		1	1 to 2 months later challenged F10 — negative
		33	32	1			6	25	

• Mild reaction

strain, reacted again when challenged with field material (F2 and F4).

These results indicate that the immune response to the primary inoculation was variable and in some cases weak. Despite these reactions, the results nevertheless suggest a close relationship between the various strains.

Tables II and IV set out results of the total inoculations carried out with the laboratory strain. Table IV presents these results in relation to the age and origin of the calves inoculated and Table II in relation to the time interval between the primary and challenge inoculations.

TABLE IV
RESULTS OF INOCULATION IN RELATION TO AGE AND ORIGIN OF EXPERIMENTAL CATTLE WITH THE LABORATORY STRAIN

Age group	Origin of cattle	Number inoculated	Inoculation reactions		Remarks
			Primary	Challenge	
Under one month	Home bred	1	−	+	Challenged when six months old
	Purchased	2	−	+	Challenged when three months old.
	Total	3			
1 to 18 months	Home bred	46	+	N.I.	
		10	+	−	
		2	+	+	
		2	−	N.I.	
		2	−	−	
	Total	62			
"	Purchased	20	+	N.I.	
		13	+	−	
		3	+	+	
		2	−	+	
		5	−	−	
	Total	43			
Over 18 months	Purchased	3	+	N.I.	
		8	+	−	
		3	−	N.I.	Two pregnant when inoculated, one aborted, both killed
		1	−	+	
		1	−	−	
	Total	16			
Summary all age groups	Home bred and Purchased	69	+	N.I.	
		31	+	−	
		5	+	+	
		5	−	N.I.	
		6	−	+	
		8	−	−	
	Total	124			

N.I. = not inoculated.

Properties of the Infecting Agent

The agent remained viable in citrated whole blood stored at 4°C. for six months, and in lymph-nodes stored at −20°C. for one month.

The agent withstood freezing and thawing five times. It was filterable through a Gradocol membrane of 590 m. A.P.D.

Lymph-nodes obtained from a calf 11 days after a temperature reaction were infective, but not those from a calf killed 88 days after reacting.

Serial passage in sheep and goats was carried out for three transfers, and the agent then transmitted back to calves.

Pigs and small laboratory animals showed no reaction following inoculation. Attempts to establish the agent in embryonated eggs have also failed.

Discussion

Diagnosis of this disease presents difficulty as there are many features in common with other conditions. In mild outbreaks with a low mortality a useful aid is that of examination of all apparently normal contacts, some of which may show high temperatures, mucoid nasal discharge or scouring usually of short duration, and ulceration in the oral cavity.

In the early stages of severe outbreaks other conditions may be suspected. Frequent drinking, rapid loss of condition, with a dirty muzzle, buccal ulceration and tenesmus are characteristic.

In chronic outbreaks intermittent scouring in a herd where there is a lack of response to anthelmintic treatment may be helpful. The prolonged course associated with the other clinical findings enumerated above and with occasional deaths is presumptive evidence of the presence of this condition.

At the moment the only diagnostic method is inoculation and cross-protection tests in calves. Attempts to develop a complement-fixation test have failed.

Differential Diagnosis

Malignant Catarrh

Eye involvement occurs with malignant catarrh, and cases tend to be sporadic. However, the main

differences are in the properties of the malignant catarrh agent which has been transmitted to rabbits (Daubney & Hudson, 1936) and in its failure to withstand freezing and thawing (Anon., 1941). Further, Piercy (1952 and 1953) failed to transmit the agent by filtrates, and also showed that it was fragile and did not withstand storage at temperatures favourable to survival of the agent recovered from outbreaks of mucosal disease.

Common Poisons

The availability of such poisons and chemical tests would establish a diagnosis.

Coccidiosis

The anterior part of the alimentary canal would not be involved. On *post-mortem* examination the wall of the caecum, large intestine and rectum are described as thickened. Response to treatment would be helpful.

Rinderpest

In wholly susceptible stock this disease would be expected to affect the whole herd but differentiation would depend upon cross-protection tests. However, the experimental incubation period is two to three days, and a high temperature persists for several days with the development of severe symptoms.

Tick-borne Fever

The natural and experimental disease are mild conditions not unlike the experimental disease described. Hudson (1950) showed that it could be diagnosed by the presence of cytoplasmic inclusion-bodies in the white blood-cells during the febrile period. We have failed to demonstrate inclusion-bodies in this disease. Further, cross-protection tests carried out have shown the two agents to be immunologically different.

Hyperkeratosis

This condition has been reported and it has been shown that it can be caused by poisoning with highly chlorinated naphthalene products. In one of the cases of suspected mucosal disease investigated, the clinical condition and *post-mortem* findings were considered to be diagnostic. Illness had followed the feeding of cake. At the time of our investigation this feeding was discontinued, an improvement in the health of the calves followed. Later, the farmer decided to finish off the cake and fed it to the same group of calves which again became ill. Unfortunately samples of the food could not be obtained for examination. Attempts to transmit the condition by inoculation using several tissues from five animals were unsuccessful.

Winter Scours

The clinical picture of winter scours differs in that normally only adults are affected and the disease spreads rapidly through the stock. Lesions are not found in the oral cavity or nares, and nasal discharge is not recorded.

Discussion

The disease under investigation needs to be compared with that of other alimentary-tract conditions, as it would appear unlikely that it is a new disease. The severe acute disease resembled rinderpest. Virus diarrhoea (New York) a disease described Olafson *et al* (1946), and a gastro-enteritis syndrome attributable to acorn poisoning cited by Völker (1950) were also considered to have features in common with rinderpest. It was shown by Olafson and Rickard (1947) and Walker and Olafson (1947) that the virus diarrhoea (New York) and rinderpest were immunologically distinct.

An outbreak of disease in Kent, bearing many resemblances to the disease encountered, was described by Simonds and Brown in 1871. It was at first suspected to be rinderpest, but finally they suggested acorn poisoning as the probable cause. In 1934 Jones questioned a diagnosis of acorn poisoning in young cattle affected with a severe haemorrhagic gastro-enteritis and suggested the disease was coccidiosis.

In 1955 Heinig described, in Germany, a malignant gastro-enteritis of cattle which resembled rinderpest. It was finally resolved that a transmissible stomatitis, associated with chlorinated naphthalene poisoning was the cause. In this case the source of chlorinated naphthalenes was a dressing used to treat binder twine. It was found that about ten yards of this twine fed to calves would cause disease. Heinig's disease differed clinically from that of American workers in that hyperkeratosis was not a feature of the German disease.

The natural disease described here resembles that recorded by Ramsey and Chivers (1953) as mucosal disease in North America. Neilson *et al.* (1955), Schipper *et al.* (1955), Pritchard *et al.* (1956), Scheidy *et al.* (1956) described conditions with many features in common with those of Ramsey and Chivers. Dow *et al.* (1956) described a similar disease syndrome in Scotland.

The experimental disease described is similar to that of virus diarrhoea (New York), as described by Baker *et al.* (1954).

Pritchard *et al.* (1955) studied the relationship between virus diarrhoea (Indiana), virus diarrhoea (New York) and mucosal disease (Ramsey and Chivers). Natural outbreaks of these conditions showed certain differences. Virus diarrhoea (Indiana) was characterised by lameness and a mortality up to 50 per cent. of affected cattle. In virus diarrhoea (New York) a high morbidity with a low mortality was usual. Frequently an abortion outbreak followed the natural disease. Mucosal disease was recorded mainly in cattle from 8 to 14 months of age. Lesions on the dorsum of the tongue and lachrymation were considered to be clinical differences from the two virus diarrhoea conditions.

By means of cross-protection tests it was shown that the agents of virus diarrhoea (New York) and virus diarrhoea (Indiana) were immunologically distinct. They suggested from the results of their preliminary experiments that the agent of mucosal disease was

also immunologically distinct from those of the other two conditions.

Summary

A disease of cattle was investigated in 10 herds. The condition was transmitted to experimental calves. A description of the symptoms and macroscopic lesions in both naturally and artificially infected calves is recorded. Transmission and cross-protection tests showed that immunity was variable and sometimes weak. The results of these tests did not disclose distinct antigenic differences.

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THE SPEAKER'S INTRODUCTION

Mr. R. A. Huck, presenting the paper, said he would like to thank the committee for giving him the opportunity to present this paper to the Congress and was sensible of the honour accorded him. Also, he wished to thank the editorial committee of the Journal of Comparative Pathology and Therapeutics for the permission to use material from his paper published in that journal. He had little to add except to say that in relation to Table 3, Farm 10, the two animals had since been challenged with a laboratory strain. In both cases there had been no reaction, indicating immunity to the laboratory strain.

Mr. Huck emphasised the opinion held by him and his colleagues that the disease was very widespread in a very mild form, and that clinically, it was possible that it would not be observed in the herd under normal conditions of management. They had encountered herds where there had been two or three deaths in a particular age group of cattle occurring over several weeks, but the animals in contact with those affected were, on inspection, apparently normal. It was only on individual examination that abnormalities were found which might be helpful in establishing a diagnosis of a mucosal disease. On examination of contacts, an animal would occasionally be found with a temperature of as much as 105 or 106° F., and there might be an accompanying mucoid nasal discharge with enlarged lymph nodes. He wished to stress that, on general inspection, nothing, suggestive of any abnormalities was seen, though, on opening the mouths of some apparently normal contacts, ulcerations in the oral cavity would be discovered. That made the disease difficult to recognise. The only positive diagnostic method at the time was by means of animal inoculation and cross protection tests.

By means of slides, Mr. Huck then took his audience on a "journey" through the alimentary canals of some of the more severe cases he had encountered.

The Openers

Mr. A. L. Wilson said: "May I first of all express my appreciation of the Committee's invitation to open this discussion and at the same time congratulate Mr. Huck on the most able manner in which he has collected so many facts into a most interesting paper. The subject is one which has received a great deal of attention during the past 3 years—so much in fact that one might be pardoned for assuming that it is a new disease. Mr. Huck states that this is unlikely and I feel that I must agree with him, but I also feel that the incidence could not have been very great in previous years otherwise it would have aroused some comment from veterinary surgeons. It would be interesting to have the opinions of members of the audience on this very point and also on the present geographical distribution of the disease in the British Isles. Mr. Huck has reported the disease in the Midlands and certain Southern Counties in England while Dow *et al.* (1956) described cases in Scotland. Since the winter of 1955-6 we have investigated in the South West of Scotland at least 40 outbreaks of a disease syndrome the main features of which have been progressive diarrhoea and emaciation with a varying degree of ulceration of the digestive tract. Mr. Huck was able to reproduce the disease at Weybridge with blood taken from one of our cases thus establishing that his disease is the same as ours. Study of the case histories and *post-mortem* reports of our cases have revealed the following facts.

Severe acute mucosal disease has been observed in approximately 5 per cent. of our outbreaks. In these the mortality rate has been up to 100 per cent., and both calves and adult cows have died. Typical of these were two outbreaks, one in Dumfriesshire and the other in Ayrshire. The former involved 6 suckled Aberdeen Angus calves and a bought-in Ayrshire heifer. The calves had been at grass all summer and were in thriving condition when housed at the end of October, 1956. All the animals became ill 5 weeks later with a nasal discharge, coughing and temperatures up to 105° F. They all had diarrhoea and salivated profusely while depression and anorexia were very marked. Many active ulcers with surrounding inflammatory reactions were found on the gums, hard palate and the nostrils. The Ayrshire heifer aborted 7 days after first becoming ill and died a fortnight afterwards while the 6 calves all died within a fortnight of first showing symptoms. At *post-mortem* examination tracheitis with ulceration of the mouth, oesophagus and abomasum were very evident. The tongue was not affected and the eyes although sunk in the head were not inflamed. A surprising feature of the outbreak was that although the mortality rate in the affected group was 100 per cent. the disease did not spread to other cattle housed in the same shed. These cases bear a striking resemblance to an outbreak described by Pritchard (1956).

The Ayrshire outbreak occurred in a pedigree beef herd and involved a 3 months old calf and two 5-year-old cows which died after an illness of 6 or 7 days. Clinically and at *post-mortem* examination they showed the typical features of acute mucosal disease.

The great majority of our outbreaks, about 95 per cent., have been of the chronic type with a morbidity rate of 25 per cent. and a mortality rate of between 9 and 10 per cent. The general picture has been one of a chronic wasting disease with intermittent diarrhoea and mucosal ulceration

which varied from a few shallow apparently non-active erosions involving the surface layers of the epithelium to extensive ulceration of the gums, tongue, nostrils, oesophagus and abomasum. The temperature rarely if ever rose above 103° F. and affected animals were always in the age group 9-24 months. *Post-mortem* examinations were carried out on 41 animals and they all showed some degree of ulceration and inflammation of the digestive tract from a mild diffuse catarrhal gastritis and enteritis to haemorrhagic inflammation of the whole surface of the affected organ. Several excellent specimens were taken from these cases and have been preserved. In one there is a linear ulcer about 4 in. long taken from the oesophagus and this, as in all the other oesophageal ulcers found, had its long axis in the sagittal plane as Mr. Huck has described. Illness in these chronic cases was very protracted and I must emphasise that most of them were examined by us after they had been treated with various anthelmintics, sulpha drugs and antibiotics, consequently it was impossible to decide if the causes had always been chronic or were a sequel to an earlier acute outbreak. On one farm 20 blue grey bullocks were outwintered on permanent pasture and began to scour in mid-February, 1955. Anthelmintic treatment was given without avail. The farm was visited in March and all 20 bullocks were still scouring and emaciated. Two cases were recumbent and these together with 5 others showed ulceration of the buccal mucosa extending to the lips and nostrils. Although there had not been any history of lameness, interdigital ulcers were present in all four feet of 3 of the animals. Faeces samples taken from the 20 bullocks gave egg counts of from 100 to 500 eggs per gramme. Four of the bullocks died and at *post-mortem* examination small active ulcers were found on the dental pad and the hard palate. In one animal there was an ulcer about half an inch in diameter on the right side of the tongue surrounded by a group of small ulcers. Haemorrhagic inflammation occurred in the rumen and reticulum, the rumen wall in particular being very thick and oedematous. Intense haemorrhagic inflammation occurred in the abomasum and small ulcers about 1 mm. in diameter were scattered over the surface. The wall was greatly thickened and oedematous, recalling, apart from the intense inflammation, the appearance of the pig's stomach in bowel oedema. Enteritis was also present although ulceration of the bowel was absent. This outbreak could probably be called an acute type but for the fact that there was an interval of from 5 to 6 weeks between the animals first becoming ill and death. The survivors recovered after a long illness.

A complicating factor in several outbreaks was the large number of parasites, particularly *Ostertagia ostertagia* and *Cooperia oncophora* recovered from cases that showed the *post-mortem* appearances of chronic mucosal disease. For instance, 17 Ayrshire calves between 6 and 9 months of age had been at grass since early May, 1956. At the beginning of June they all developed a watery diarrhoea and treatment for parasites was given. When the farm was visited a fortnight later all the animals showed active ulceration of the mouth and tongue and were still scouring. There was no rise in temperature. Faeces samples gave egg counts of from 200 to 4,700 e.p.g. Two calves were moribund and were collected for *post-mortem* examination. Active ulceration was found in the buccal mucosa and on the tongue, while the abomasum was inflamed, thickened and showed many small ulcers. A total worm count produced 13,650 and 13,000 worms respectively with *O. ostertagia* and *C. oncophora* predominating. The surviving 15 animals remained ill for several weeks despite treatment with anthelmintics, penicillin, streptomycin and penicillin, and 5 eventually died in August from parasitic bronchitis.

Treatment has never been successful and animals have lingered on often for months despite all attempts to fatten them with appetising foods.

Diagnosis of the acute type although difficult is less so than with the chronic type. In our experience there is a sudden onset with scouring and obvious ulceration of the buccal cavity for the examination of which a hand torch is most useful. The temperature is usually about 105° F.

In the chronic types scouring with or without excessive salivation are often the first signs of illness and since the scour is usually imputed to parasitism the animals receive treatment with an anthelmintic. In such cases the entire stock must be examined and it is surprising how many ulcers may be seen in the mouths of animals that are not obviously ill. Worm egg counts are not of great value particularly since the animals will have been treated with an anthelmintic. Even at *post-mortem* examination a definite diagnosis cannot be made until all other conditions such as Johne's Disease, salmonellosis and parasitism have been ruled out. Accurate diagnosis at the moment—as Mr. Huck has mentioned—depends on inoculation tests in susceptible calves. Finally, it has been suggested that mucosal disease might be confused with acorn poisoning, but the description of the latter given by Tailhardat (1952) does not in any way resemble mucosal disease.

Summarising our experiences it would seem that the number of acute outbreaks has been relatively small and that most cases have been of a chronic nature. Mild outbreaks unaccompanied by serious illness are probably very common and mucosal disease is only suspected after finding ulcers in the mouth.

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Dr. A. O. Betts (University of Cambridge) who, with Mr. Wilson opened the discussion, congratulated Mr. Huck both on his excellent paper on an important subject and on his courage in tackling such a difficult and complex problem. Clinically, he said, the American workers recognised several mucosal diseases of cattle and tended to use the term " mucosal disease complex " to cover the whole group. One of the mucosal diseases, infectious bovine rhinotracheitis, was essentially a respiratory disease and seemed to be clearly differentiated from those mucosal diseases affecting primarily the alimentary canal. In the latter group they included the mucosal disease of Ramsey and Chivers, virus diarrhoea (New York) of the Cornell workers, and the various strains of virus diarrhoea (Indiana) of the Purdue workers. Perhaps the condition reported from Sweden under the name of epizootic enteritis of cattle belonged also to that group.

Clinically, virus diarrhoea and mucosal disease were closely similar, and Dr. Pritchard of Purdue University had said in a paper " the actual or apparent differences between these diseases are more quantitative than qualitative differences. In other words, the differences are more a difference in degree than differences in kinds of signs and lesions." In the United States there was currently quite a lively controversy as to whether mucosal disease and virus diarrhoea were separate diseases or merely different manifestations of the disease, and the fact that Mr. Huck's experimental disease resembled virus diarrhoea, although the infectious material came from mucosal disease-like conditions, might be significant. It would not be easy however, to determine conclusively whether the various mucosal diseases were related. As both Mr. Huck and the American workers had shown, the causal agents were antigenically fickle, to say the least. Moreover, the Purdue workers claimed to have demonstrated, in spite of the difficulties, immunological differences between strains of virus diarrhoea (Indiana) itself.

Mr. Huck, said Dr. Betts, had pointed out some of the difficulties of using calves as experimental animals. Quite apart from the expense of using calves, other difficulties arose when the natural host was used for studying a widespread disease such as that under review. It might be difficult to obtain uniformly susceptible calves which did not have some degree of active or passive immunity. Moreover, there was the ever-present problem of intercurrent infections. For any major advances to be made it was thus necessary to find a simple way of cultivating the causal agent. In that connection, Mr. Huck had said in his paper that no reaction was obtained in pigs. Had he tried very young pigs? The Purdue workers were able to infect such animals with virus diarrhoea and produce diarrhoea, and had, incidentally, reported the establishment of infection in rabbits. Again, had tissue culture methods been used at Weybridge for the cultivation of the causal agent?

There had recently been reports from the U.S.A. of the growth in tissue culture of agents from the " alimentary " group of the mucosal disease complex, while the virus of infectious bovine rhinotracheitis was the kind of virus that tissue culture workers dreamed about. In conclusion, he wished to ask if Mr. Huck had any comments to make on the suggestion that mucosal disease might be virus diarrhoea plus a vitamin A deficiency.

Dr. Betts used a number of slides and a film to illustrate his contribution to the discussion.

The General Discussion

Dr. R. E. Glover (London). Mr. Huck had noted that normal calves in contact with natural cases of the disease become infected whereas no transmission occurs between experimentally-infected and normal animals. He also mentioned that the agent was transmitted by intravenous, subcutaneous and intraglandular routes; the respiratory route was not listed. Possibly the latter has been tried with negative results. Would Mr. Huck comment on the possibility that the virus can infect the respiratory tract without necessarily inducing gross lesions and that transmission may occur in this manner.

A second point concerned the experimental transmission to sheep and goats—a most important observation. As no mention was made of the lesions produced, could it be assumed that they were similar in character and extent to those seen in cattle? If this was the case, the disease in sheep might present even greater problems of differential diagnosis than cattle.

Mr. Esmonde Little (Dublin). The mucosal disease as described by Mr. Huck, and the very excellent slides illustrating the mouth lesions, are almost identical with a condition of young stores, which was investigated in Ireland just after the severe outbreak of foot and mouth disease, 1912-13. This condition was detected among young stores at Liverpool, which had been shipped from Ireland, and all shipments were held up for some time, as it was at first thought to be a mild form of foot-and-mouth disease. Animals were traced back to the farms of origin in Ireland, which were situated in the vicinity of Armagh—and the conditions at that time was known as " Armagh Disease." No cases of foot-and-mouth disease were found on the farms concerned, as on the examination of numerous young stores in the County Armagh. The condition was found to be not uncommon. The tongue lesions were, on cursory examination, not unlike those of foot-and-mouth disease, except there was no evidence of any bleb, but the superficial layer of epithelum was slightly raised in patches and could easily be stripped off, but there was no exposure of the underlying tissue. The condition was investigated at the time by Professor Mettam, and Mr. Little believed there was a report published at the time in the Journal of the Department of Agriculture.

Mr. R. M. Gambles (Nigeria). I should like to ask Mr. Huck whether he considers that the virus of mucosal disease may be related to, or identical with, that of other conditions previously described under different names. I am struck with the resemblance of some of the lesions to those of bluetongue of sheep, and although this disease is not believed to cause symptoms in cattle there are other similar conditions which have been confused with it. Bluetongue virus was isolated in S. Africa from cattle in a bluetongue endemic area suffering from what had been called " pseudo-foot-and-mouth disease," and this was then thought to be bovine bluetongue. In 1940 Mason & Neitz showed that this was a separate entity which they called " Erosive Stomatitis," and that the previous confusion had been due to the accidental presence of the bluetongue virus. More recently Komarov & Goldsmith have reported bluetongue in both sheep and cattle in Israel, but this may be a similar occurrence to the S. African cases. Does Mr. Huck think it likely that it may be mucosal disease which has been occurring in S. Africa and Israel?

The Reply

Replying to the discussion, Mr. Huck referred to Mr. Wilson's statement that all ages were involved in the acute types of outbreak, but he had found that in these cases the one outstanding feature had been that a particular age group of animals had been affected. As to acorn poisoning, of the two types described by Jones in 1934, he referred to the severe haemorrhagic type as particularly affecting young cattle.

In reply to Dr. Betts, he was at the moment unable to saw what was the relationship between mucosal disease and virus diarrhoea, except that the naturally severe disease experienced in this country was very similar to mucosal disease as described by Ramsey and Chivers, whilst the experimental work carried out here very closely resembled that carried out by Baker and his colleagues in New York. From Table I it would be seen that the disease was encountered in grazing and housed stock throughout the year. It was, therefore, unlikely that avitaminosis played a part in the disease syndrome. It was true that, using the special technique of alternating passage, Baker and his colleagues had established the agent of virus diarrhoea in rabbits. However, it must be made quite clear that the rabbit was of no value as an indicator of the condition, as no disease followed inoculation.

With regard to the route of infection, they had tried by nasal installation to infect two young calves. The calves had not reacted, although they were later proved susceptible, though the fact that they were very young may have clouded the issue as failure had so far attended attempts to infect very young animals. Animals of 2 months and over could, apparently, be infected successfully. Various aspects of the study had been pursued by using sheep, but the workers got a lot of what are now called non-specific reactions. In one case where it was thought there had been reaction to inoculation, the material from the sheep had failed to produce a response in calves, and sheep had to be abandoned experimentally. The same applied to goats. Where an agent was recovered from sheep, however, they had scouring of short duration, and enlarged lymph nodes.

Lachrymation had not been observed, at least not as a primary symptom, nor had any affection of the vulva been noticed, though where there was dribbling of mucoid material it was quite possible that there would be inflammation of the vulva. Two pregnant animals had been inoculated with infected material and, though no reaction had been observed, one of the animals aborted two months later. Both were killed. The agent was not recovered from foetal tissues.

Mr. Huck said that he had no personal experience of bluetongue, but the first thing that had struck several of his colleagues and himself on seeing the film was the close resemblance of that disease to the clinical picture of a mucosal disease in cattle. They had not tried to determine the relationship experimentally. They had not come across stomatitis, though the Germans had isolated what they considered to be a specific stomatitis agent which did not cause alimentary tract lesions. Again, the fact that several of the cases examined had first been investigated for foot-and-mouth disease obviously showed there was some resemblance in the clinical picture.

Physiological Foundations of Milk Production and Lactational Disorders

BY
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LACTATION is a complex phenomenon which depends directly or indirectly upon almost every system of the body. For example, the digestive system and liver supply the precursors of the milk, the circulatory system transports these to the secretory cells of the mammary gland, the endocrine system regulates in great part growth, metabolic and contractile processes in lactation, and the nervous system participates in at least two important reflexes in suckling or milking. This article aims to scan present knowledge of lactational physiology and touch on some applications in dairy production and veterinary medicine.

Roots of Lactational Performance

Fig. 1 illustrates in schematic form the major factors controlling the secretory output of the udder. It should quickly be apparent that hormones, though they intervene in mammary development, secretion and ejection of milk, are not the sole arbiters of lactational efficiency. Nevertheless endocrine physiology will necessarily predominate in the ensuing discussion. Nutritional and genetic influences are outside the scope of this paper, and the limiting effects of management or disease will receive mention in later sections.

Direct evidence that the number of secretory cells determines the rate of formation of milk has come from the work of Richardson (1953), who evolved a method for measuring the total alveolar surface area. In a series of goats whose udders were developed by hormone administration he found that ensuing milk yields were proportional to the calculated total areas of the alveolar epithelium. Since the latter reflect the adequacy of mammary growth processes we must first consider how development of the glands is produced.

Until puberty the mammae grow at the same rate as the surrounding integument, and the parenchyma is represented by a rudimentary duct system sprouting from a cistern at the base of each teat. Differential growth commences at puberty under the combined influence of anterior pituitary and gonadal hormones. Apart from the gonadotrophins F.S.H. and L.H., which are responsible for managing the ovarian cycles, replacement experiments in hypophysectomised animals indicate that prolactin and growth hormone are essential for normal mammary growth (see for example, Lyons, Johnson, Cole & Li, 1955). There appears to be insufficient evidence for the existence specific pituitary "mammogenic hormones" separate from the six established anterior pituitary hormones. But there is good reason to suppose that in some species at least the placenta elaborates hormones which contribute to the growth and secretory changes occurring in late pregnancy (Leonard, 1945).

Though species differences undoubtedly exist (Folley, 1956) there is broad agreement that of the ovarian contributions oestrogen acts predominantly on the duct system, while progesterone mainly stimulates alveolar growth. Nevertheless both hormones are probably essential for proper glandular development. A variety of histological abnormalities, including dilated alveoli and epithelial papillomata, have been described in the udders of goats, heifers and cows following treatment with oestrogens, either alone or with deficient amounts of progesterone (Sykes & Wrenn, 1951; Cowie, Folley, Malpress & Richardson, 1952). As might be expected the milk yields obtained from such udders are markedly subnormal.

Once in being the secretory epithelium needs to work. The terminal stages of mammary growth during pregnancy merge with the onset of the secretory phase. Thereafter the maintenance of the alveolar system depends largely upon the continuance of secretory activity. To this extent growth and secretory functions are inseparably linked. The decline of secretory activity at the end of lactation is accompanied by involution of the mammary parenchyma. The connexion is seen even more dramatically when milk removal is prevented. After a variable period of alveolar engorgement secretion is halted, the milk thickens and becomes resorbed, and the alveoli collapse and disintegrate. A recent study by Silver (1956) has revealed that during the stage of engorgement in the rat a marked constriction occurs in the capillary vessels surrounding the alveoli with virtual exclusion of blood from the capillary bed. Since the constriction remains until almost all the milk residue has been resorbed it is likely that this resorption occurs by way of the lymphatics. After the alveoli collapse the capillary vessels open up again and connective tissue invasion of the degenerating alveoli commences.

Having thus focused attention on the importance of milk removal for the structural and functional integrity of the alveolar epithelium, we shall next consider the mechanisms by which evacuation of the mammary gland is brought about; then proceed to the much less well understood problem of the control of milk secretion.

The phenomenon of milk ejection (less appropriately termed "let-down") is well appreciated in agricultural circles as an essential prerequisite for efficient milking. It is associated with the expression of milk from the alveoli down the lactiferous ducts into the

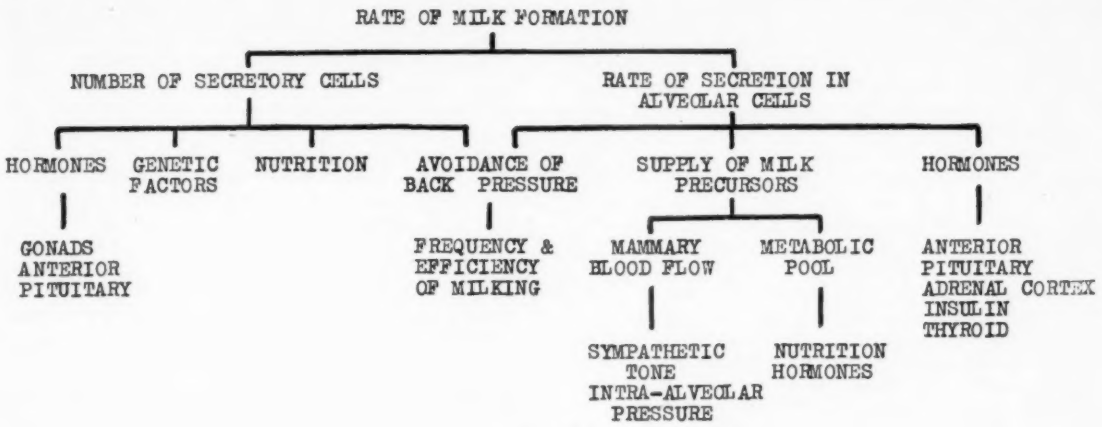

FIG. 1.

distensible udder cisterns, where the resulting rise in pressure may force milk past the teat sphincters to the exterior. The contractile tissue producing this effect is now known to be the extensive system of myoepithelial cells which invests the alveoli and ducts (Richardson, 1949; Linzell, 1952, 1955). The arrangement of these cells is such that their contraction compresses the alveoli and widens the ducts.

Earlier theories relying on a spinal reflex mechanism for milk ejection were proved inadequate when Ely & Petersen (1941) demonstrated that the response survived motor denervation of the udder. The view put forward by these authors that milk ejection depends upon a reflex release of oxytocin from the posterior pituitary gland has received abundant experimental confirmation (Cross, 1955a; Cowie & Folley, 1957). Thus, for example, electrical stimulation of the hypothalamic pathways to the posterior pituitary gland elicits typical milk ejection responses (Andersson, 1951; Cross & Harris, 1952) while interruption of these pathways abolishes natural milk ejection (Cross & Harris, 1952). Oxytocin appears to be the physiological milk-ejecting hormone since it is about six times more active than vasopressin, and there is evidence that the latter is not released in sufficient amount by the stimulus of suckling or milking to affect the mammary myoepithelium (Cross, 1951; Cross & Van Dyke, 1953).

Certain properties of this neuro-hormonal mechanism deserve mention. In most species the interval between the suckling or milking stimulus and the start of milk ejection is about half to one minute, and the ejection phase seldom lasts more than a few minutes. In the cow (but not the sow) the reflex is readily conditioned to stimuli, such as washing the udder, which habitually precede actual milking. Disturbances of the reflex can result from a variety of causes. Narcotic drugs by depressing central excitability may inhibit the reflex release of oxytocin. Thickening of the milk, which can result from a prolonged non-milking interval or inflammatory changes, interferes with the free passage of the milk through the ducts. Constriction of mammary blood vessels, whether provoked by sympathetic excitation (*e.g.*, in cold, emotional stress or following haemorrhage) injection of drugs (adrenaline or vasopressin) or by engorgement of the mammary glands (see above) impairs milk ejection by preventing access of oxytocin to the contractile tissue. Hypocalcaemia decreases the responsiveness of the myoepithelium. Finally emotional disturbance blocks the reflex secretion of oxytocin. Some of these relationships are illustrated in Fig. 2.

It is of interest that the myoepithelium responds to mechanical stimuli applied directly to the mammary glands (Cross, 1954a) and while this mechanism probably plays little part in normal milk removal it can be of diagnostic value in confirming the capacity of the effector tissue to eject milk.

Note has been taken in the preceding discussion of the limiting effects of the degree of alveolar development and efficiency of milk removal on the rate of milk production. There remain two further processes of primary importance in lactational performance. They are the supply of milk precursors to the secretory elements and the influences operating at the alveolar level to stimulate synthetic activity. Fig. 3 indicates present views on the hormonal control of these two processes. But it must be admitted that though the principal endocrine secretions influencing milk secretion have been identified, we know remarkably little about their mode of action.

In the first place it is clear that ovarian hormones are not essential to the secretory phase of lactation; indeed ovariectomy may prolong lactation. However, most of the remaining endocrine glands appear to play important roles in milk secretion. Hypophysectomy quickly terminates lactation, and the pancreatic islets also appear to be indispensable. Removal of the adrenals, thyroid and parathyroids severely impair lactational performance though secretion may not be completely arrested (see review by Folley, 1952).

Evidence from the injection of prolactin into the mammary duct system indicates that this hormone directly stimulates milk formation (Lyons, 1942; Bradley & Clarke, 1956). Extracts rich in other pituitary activities do not have this action. This

observation may be more relevant to the initiation of milk secretion (lactogenesis) than to its maintenance (galactopoiesis) for a long series of experiments have failed to show any notable stimulating effect of purified prolactin on established lactation. In fact the pituitary growth hormone seems to be much the most active in this regard (Cotes, Crichton, Folley & Young, 1949). By contrast ACTH injections depress milk yield in cows (Flux, Folley & Rowland, 1954) though as indicated above an adequate supply of adrenocortical hormone is necessary for milk secretion.

Metabolic studies with mammary slices suggest that growth hormone, insulin and cortisone as well as prolactin may influence one or other of the biochemical activities of the mammary gland (see Folley, 1956). Another technique holding out great promise for analysis of direct hormonal control of alveolar secretion is that of the isolated perfused udder, though there are many technical difficulties to be overcome (Silver, 1952). Recently a completely different approach to the problem of the site of hormonal action has been made by Cater, Phillips and Silver (1957). These Cambridge workers have recorded characteristic and reproducible changes in the *p*H, oxygen tension and oxidation-reduction potentials of intact mammary tissue in rats following injection of various hormones. Alterations of redox potential occurred within two minutes of intravenous injection of growth hormone, water soluble oestrogen, and desoxycorticosterone. After insulin injection the response was delayed for 8 to 10 minutes, *p*H changes accompanied the redox responses to insulin and growth hormone. Oestrogen produced a marked effect on oxygen tension which increased by up to 50 per cent. over about 15 minutes. Control readings from muscle electrodes were either unchanged or when present (*e.g.*, with insulin) much smaller than the mammary responses. Clearly, however, much remains to be done before particular roles can be assigned to the various hormones known to be involved in the secretion of milk.

The importance of the neural stimulus of suckling or milking in relation to milk ejection has been discussed above. It is also generally accepted that this stimulation is concerned too in the secretion of anterior pituitary "lactogenic" hormones (Folley, 1952). Thus the suckling or milking stimulus is believed to play a central part in both secretion and ejection of milk. Recently evidence has accumulated that these two neuro-endocrine mechanisms may be more intimately linked than previously supposed. Benson and Folley (1956), (see also Cowie & Folley, 1957) have shown that oxytocin injections retard weaning involution in rats—an effect characteristic of prolactin. These authors suggest therefore that oxytocin liberated in response to the suckling stimulus may be the humoral excitant to anterior pituitary secretion of lactogenic factors. In this connexion it may be noted that several workers (*e.g.*, Donker, Koshi & Petersen, 1954) have found that repeated oxytocin injections in cows may produce sustained increases in milk yields, of an order too large to be readily accounted for in terms of more efficient evacuation of the udder.

Applications in Dairy Management and Production

In this section some aspects of milking technique will be considered in the light of present knowledge of the physiology of milking. This will be followed by a discussion of the use and limitations of hormone administration in the stimulation of milk production.

It is a commonplace that cows display highly individual milking characteristics. Such expressions as "slow milker," "strippy cow," etc., bear testimony to this fact. What is known of the physiological processes underlying these differences? Leaving aside the operation of the milking machine itself, which clearly is not concerned in variations between cows, there are two factors controlling milking performance (see Fig. 2). These are the patency of the teat and mammary ducts, and the milk-ejection reflex. Tight teat sphincters inevitably slow down milking, with the effect that milk ejection begins to subside (drop in cistern pressure) before the full yield of milk can be withdrawn. In such cases the limiting factor is anatomical and nothing much can be done about it.

But in the absence of this defect wide variations in the milk flow rate occur in different cows, and indeed in the same animal at different periods of lactation (Foot, 1935). Almost certainly such variations reflect individual differences in the characteristics of the milk-ejection reflex. In general the maximum rate of flow is reached in about two minutes. High flow rates are associated with high milk yield, and a simple index of milking performance is given by the percentage of the total yield obtained in two minutes (Beck, Fryer & Roark, 1951).

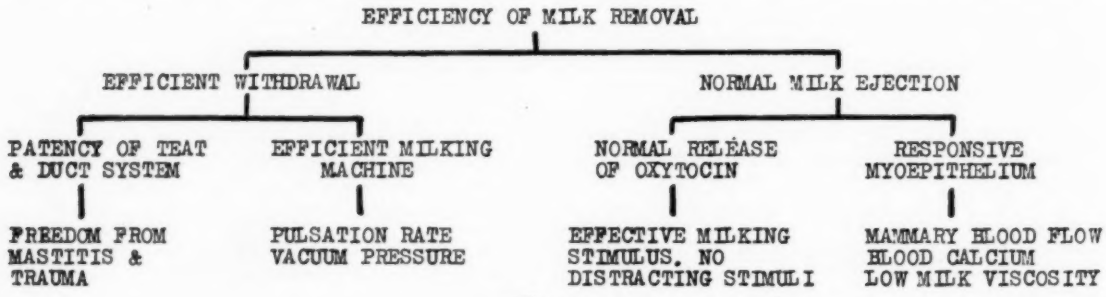
EFFICIENCY OF MILK REMOVAL
EFFICIENT WITHDRAWAL
NORMAL MILK EJECTION
PATENCY OF TEAT & DUCT SYSTEM
EFFICIENT MILKING MACHINE
NORMAL RELEASE OF OXYTOCIN
RESPONSIVE MYOEPITHELIUM
FREEDOM FROM MASTITIS & TRAUMA
PULSATION RATE VACUUM PRESSURE
EFFECTIVE MILKING STIMULUS, NO DISTRACTING STIMULI
MAMMARY BLOOD FLOW BLOOD CALCIUM LOW MILK VISCOSITY

FIG. 2.

At this point it would be well to consider again the relation of the milking operation to the milk-ejection reflex. As mentioned in the preceding section, milk ejection in the cow normally occurs as a conditioned response to the stimulus provided by the preparation of the udder. Since the ejection response is short-lived it is obviously desirable to start milking out immediately ejection occurs (*i.e.*, about one minute after stimulation) so as to derive the maximum advantage from the transitory rise in intramammary pressure. Several workers have found that delay in the application of the teat cups reduces the milk yield (Miller & Petersen, 1941; Ward & Smith, 1949). The difference is not great, however, and some have denied its existence (Knodt, Reid, Williams & Kesler, 1949).

A possible explanation of these results may be found in the work of Whittlestone (1951, 1954) using an electronic device for accurate recording of milk flow rates. This author has described a condition of "double ejection" which may occur when the conditioning stimulus is inadequate or when the start of milking is delayed. Here the initial flow of milk suddenly ceases after a minute or two and is then followed by a further flow. The second flow he believes to be due to the (unconditioned) stimulus provided by the action of the milking machine on the teats eliciting a further release of oxytocin. Thus a delay of several minutes before milking is commenced may result in a short initial flow representing the tail end of the conditioned milk ejection response and a longer second flow due to response stimulated by actual milking. Another variety of double ejection can be produced by vigorous machine stripping, since this too serves as an adequate stimulus for a second milk-ejection response. In this way "strippy cows" are made. Double ejection is to be avoided since it reduces milking efficiency by lengthening milking time. It also increases the tendency to "crawling" of the teat cups (Petersen, 1943), which besides impeding outflow of milk from the udder cisterns, increases trauma to the udder, thus predisposing to mastitis.

The need for tranquil conditions in the milking shed is generally appreciated. Ely and Petersen (1941) who studied the effect of emotional disturbance experimentally in cows, came to the conclusion that a peripheral block of milk ejection occurred in the udder as a result of the secretion of adrenaline. It is unlikely, however, that endogenous secretion of adrenaline would produce sufficient blood concentrations to exert this effect (Cross, 1955b). Moreover, the experiments of Whittlestone (1951) who inhibited the milk-ejection reflex in cows by electric shocks conform better with the idea that the emotional disturbance causes a central inhibition of the reflex release of oxytocin. It is of great practical interest that such shock treatment in some cases produced a fairly permanent inhibitory effect persisting for several weeks in the absence of further shocks.

Before discussing some of the work that has been carried out on the application of hormone administration in milk production it would seem desirable to emphasise that the animals concerned are in normal health. Any exogenous supplies of hormone will be in excess of the normal physiological requirement and the animal usually responds by adjusting its physiological economy in such a way as to minimise the effects of the administered hormone. If the dose given is too great for homeostatic adjustment by the animal the chances of undesirable side actions are increased. These and other hazards of hormone administration have recently been discussed (Cross, 1954b).

The wartime need for maximum production of milk stimulated much pioneer work on the effects of various hormonally active preparations in dairy animals. Much of this research, principally concerned with synthetic oestrogens and thyroactive substances was published as collected papers in Volume IV of the *Journal of Endocrinology* (1944-6).

Perhaps the most dramatic finding was the induction of lactation by subcutaneous implants of oestrogens in unbred or non-fertile heifers and cows (see also Malpress, 1947). The lactational response was somewhat variable, but about half the treated animals produced economic yields of milk, and in a much shorter time than would be required for normal pregnancy. However, a disconcerting proportion of subjects showed nymphomaniacal symptoms and the associated coital mimicry gave a high incidence of pelvic fractures. A further disadvantage was the need to remove the implants after the establishment of milk production to prevent a subsequent depression of yields. It is possible that one source of the variation in response was the endogenous output of progesterone. As we have noted in the previous section, oestrogen alone does not induce normal glandular development. A regime of treatment incorporating progesterone in suitable ratio with oestrogen might hold out better prospects, both of more uniform lactational responses and of minimising undesirable behavioural sequelae, but in view of the dangers of prolonged oestrogenisation to subsequent breeding performance, the application of such treatments seems likely to be limited to high producing cows that have become sterile.

Much less work has been done on the artificial induction of lactation in sheep, though the potentialities of the technique for the rearing of orphan or twin lambs on barren foster ewes has been emphasised recently by McPherson (1955). This author reported that a single injection of 40 mg. stilboestrol produced an abundant flow of milk within seven days. However, an attempt to repeat this work in New Zealand (Lambourne, 1956) was less successful. Though some mammary development occurred the milk yields were disappointing—less than 1 lb. daily.

There is now much evidence (reviewed by Blaxter, 1952) that the oral administration of thyroproteins (*e.g.*, iodocasein) or thyroxine can produce striking increases in the milk yield of cows, particularly when given in the declining phase of lactation. Pure thyroxine is a preferable agent to iodoproteins, since the latter possess a variable activity and free iodine content; also a limited palatability. But neither treatment is free from hazard. High dosage or prolonged administration has an adverse effect on lactation and a large number of undesirable side actions have been reported, including increased pulse and

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respiration rate, loss of weight, unthriftiness and diarrhoea, hyperexcitability and tremor, bony changes and increased calf mortality.

It seems likely that the galactopoietic action of thyroid hormone is attributable to its general stimulation of metabolism rather than to any specific effect on milk synthesis. The extra production of milk may, therefore, be accompanied both by an increased food intake and by loss of bodyweight, indicating a decreased efficiency of conversion of foodstuffs to milk (Reece, 1950; Thomas & Moore, 1953). It is possible that an increased ration alone would produce the same milk increment more economically. Many workers have reported that the galactopoietic response is temporary (*e.g.*, Aitken, Boyne & Crichton, 1953) and often followed by a decrease in production below control levels. These findings are explicable in terms of known principles of thyroid physiology. Exogenous supplies of thyroxine are offset by decreased secretion of thyrotrophic hormone so that endogenous output of thyroxine drops. When the exogenous source is stopped there is a temporary hypothyroid state until the thyrotrophic hormone secretion picks up to normal. Therefore chronic hyperthyroidism results only when the daily dose of thyroxine in the feed exceeds the normal endogenous output. Amounts below this produce only a temporary hyperthyroidism, and after things have reached equilibrium the animal's own thyroid gland

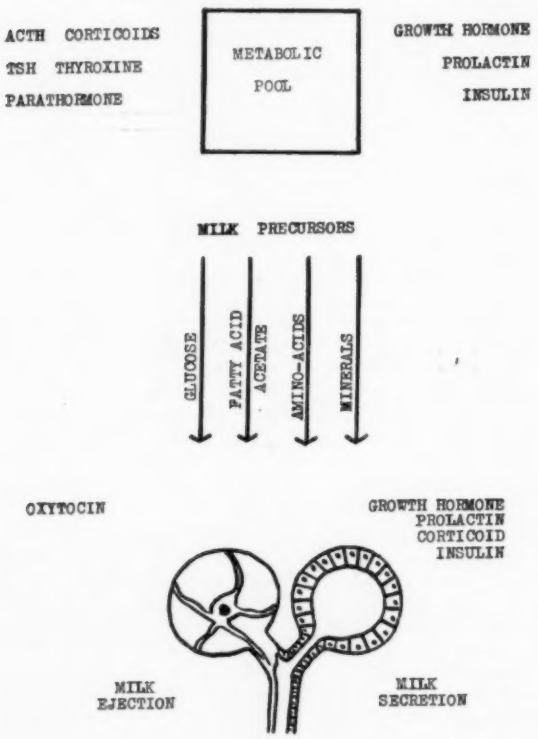

FIG. 3.

remains in a depressed state for the duration of the treatment. The largest field trial so far reported is that of Leech and Bailey (1953) which involved 2,000 cows over three years. Apart from a small increase in "digestive complaints" no untoward effects were observed to follow eight-week periods of treatment with 15 g. iodocasein daily. This regime resulted in a 3 per cent. increase in total milk yield. This dose is probably below the equivalent normal endogenous thyroid output so that the homeostatic mechanism just described would have minimised hyperthyroid effects.

Reference has been made earlier to the emergence of growth hormone as the most potent galactopoietic principle in anterior pituitary extracts. In a recent well controlled study on identical twin Jersey cattle Brumby and Hancock (1955) demonstrated the superiority of growth hormone over thyroid treatment as a means of stimulating milk production. A daily dose of 50 mg. growth hormone given by subcutaneous injection significantly raised milk yields above those in both thyroxine treated and control animals. The treatment was equally effective at the peak period or in the declining phase of lactation. In contrast to the findings with thyroxine administration, growth hormone resulted in a net increase in the efficiency of conversion of foodstuffs to milk. There was no loss of weight, and the reverse swing in milk production following cessation of the treatment characteristic of thyroxine, was absent. Despite the diabetogenic effects of growth hormone seen in dogs and cats these workers found no change in the blood levels of glucose or ketone bodies. In a later study Brumby (1956) failed to confirm a suggestion (Chung, 1955) that pre-partum treatment with growth hormone increased the subsequent milk yield. In view of the obvious potentialities of this hormone for stimulating milk production it is unfortunate that it suffers from two serious practical disadvantages, *viz.* its high cost and the fact that it cannot be administered in the feed.

Applications in Veterinary Medicine

Some conception of the various ways in which lactation may become deranged can be gleaned from the relationships indicated in Fig. 1. Agalactia or hypogalactia may result from mammary hypoplasia, originating in turn from genetic, nutritional or endocrine causes, or combinations of these. Failure of established lactation may result from alveolar engorgement, nutritional, hormonal or metabolic upsets, or again from tissue inflammation and destruction consequent upon invasion of the udder by pathogenic organisms. Because of the inherent complexity of these possible disease mechanisms, and the wide area of ignorance, particularly of the detailed orchestration of the mammary secretory process, accurate diagnosis of lactational disorders presents many difficulties. A logical first step, however, would be to differentiate between primary secretory failure due either to inadequate mammary development or to disturbances of milk formation, and secondary secretory failure due to some interference with the milk-ejection mechanism. In this section some common disorders of lactation will be briefly discussed

with main reference to existing ideas of their pathological physiology and rational therapy.

In its commonest form bovine ketosis is a disease of lactation. The lactational defect is primary secretory failure associated with hypoglycaemia and hyperketonaemia. According to Shaw and his group, who have studied the condition extensively, it is caused by adrenocortical insufficiency. More particularly these workers regard primary ketosis as a "disease of adaptation" in the terminology of Selye, brought about by the "stress" of parturition. The clinical symptoms appear in the "stage of exhaustion" in which the pituitary fails to secrete enough ACTH to maintain an adequate output of adrenocortical hormones. Much evidence is adduced in favour of this theory (Shaw, Hatziolos, Leffel, Chung and Gilbert, 1953) but as many of the reports are published only in abstract form it is difficult to evaluate critically. Between one-third and one-half of ketosis cases were stated not to respond to glucose therapy, but 75 ketotic cows treated with one to three injections of 1.5 g. cortisone fully recovered. Failure to respond to cortisone, in fact, was considered to rule out a diagnosis of primary ketosis. Hydrocortisone was even more effective in a dose of 300 mg. Long acting ACTH proved effective in a dose of 600 units. From autopsies on 14 ketotic cows enlarged and degenerating adrenals, regression of the anterior pituitary gland, involution of the thymolymphatic system and pancreas, gastrointestinal inflammation and ulcers, nephrosis and fatty livers were reported. It is surprising that animals with such widespread pathology should respond so promptly to cortisone treatment; more so in view of the degeneration of the adrenals that they should respond to ACTH. Experimental support for the postulated exhaustion of the pituitary ACTH releasing mechanism came from tests in seven ketotic cows which showed only slight changes in blood eosinophils following a test injection of adrenaline, whereas 13 unaffected post-parturient animals reacted by marked eosinopenia. Since the validity of this test of pituitary ACTH release has not been established for the cow, it would be preferable to have evidence from estimation of blood levels of adrenal corticoids in bovine ketosis, especially as some workers believe the adrenocortical changes seen at autopsy reflect normal hypertrophic changes, *i.e.*, indicating a hyperfunctional rather than a hypofunctional state (*cf.* Dye, Roberts, Blampied & Fincher, 1953). Indeed a recent study involving estimation of plasma 17-hydroxycorticosteroid in bovine ketosis subjects did give results which indicated higher than normal blood concentrations of adrenocortical hormone (Robertson, Lennon & Mixner, 1955). This finding seems to have prompted a re-orientation of Shaw's views (Shaw, 1956) according to which the adrenal insufficiency may be relative, *i.e.*, partly dependent on the inability of the tissues to utilise adrenocortical hormone. One factor in this failure of tissue utilisation may be hypothyroidism as suggested by results obtained by Robertson *et al.* (1955). It seems, therefore, that the essential nature of primary ketosis remains to be determined.

Milk fever (parturient paresis) is another familiar disease of lactation in cows. Hibbs (1950) in an absorbing but chastening review has described 30 separate theories of the aetiology of milk fever. They range from cerebral congestion through anaphylaxis and avitaminosis to parathyroid deficiency. It is difficult to believe that so many people can have been so wrong so often. Blushes would have been spared if many of the hundreds of theorists cited in this review had awaited the provision of unequivocal evidence. Only two theories will receive mention here. The first is perhaps the most widely held; that milk fever is due to parathyroid dysfunction. The second, and most recent contender, is that milk fever, like ketosis, is a "disease of adaptation."

When the correlation of milk fever symptoms with low blood calcium levels was first discovered (Little & Wright, 1925) it was perhaps natural that the parathyroid gland should be indicted (Dyerre & Greig, 1925). However, surprisingly little evidence has been forthcoming since that time to incriminate that gland. Parathyroid therapy for instance was found to be of doubtful value in the condition (Mattick & Little, 1933). Much research has been carried out on the calcium and phosphorus changes in the blood of normal parturient and milk fever cows, the burden of which is that the syndrome results from the occurrence in exaggerated form of a natural trend towards low blood calcium and phosphorus in the parturient animal (*e.g.* Duckworth & Godden, 1940). It is also well established that udder inflation reverses this state and returns blood levels to the normal range (*e.g.* Niedermeier & Smith, 1950). The superiority of this form of therapy over calcium injection in some milk fever cases may depend upon its ability more rapidly to correct an associated hypophosphataemia (Robertson, Burgess, Marr & Milne, 1948). How udder inflation produces these changes is obscure. There is perhaps a slight balance of the evidence in favour of a reflex nervous effect rather than simply a restraint on calcium loss in milk. In this connexion it should be noted that so far no one has demonstrated that the parathyroid gland can be brought under nervous control. Its secretory activity appears to be almost entirely decided by the plasma calcium concentration.

So far then we have no firm indications of parathyroid involvement in the aetiology of milk fever. Quite recently, however, experiments of unusual interest, bearing on this problem, have been performed by Boda (1956), (see also review by Boda & Cole, 1956). The principle of the experiments was that if cows were kept on a low calcium high phosphorus diet during pregnancy the parathyroid gland would become hypertrophic and, therefore, presumably, better able to maintain an adequate blood level of calcium after parturition. Three such diets were fed during the last two to three months of pregnancy to a total of 72 cows. Whereas 27 of these previously had milk fever, only five showed symptoms on the low calcium diet. The opposite test of the principle would be to feed high calcium diet during pregnancy in order to induce a functional atrophy of the parathyroid gland. This procedure has now been reported to increase the incidence of milk fever (Ender, Dishington & Helgeborstad, 1956). These results seem to provide the first strong circum-

stantial evidence linking parathyroid function with milk fever.

One aspect of the symptomatology of milk fever may be singled out for mention here. A common feature of the condition is a diminished or absent milk ejection during milking. Whether hypocalcaemia has any interfering effect on posterior pituitary release of oxytocin is unknown; but this particular symptom would seem to be adequately explained by the depressant effect of hypocalcaemia on the mammary myoepithelium (Peeters, Massart & Coussens, 1947).

The view that milk fever is due to adrenocortical hypofunction (Garm, 1950) has found some support. Smith and Merrill (1954) found very low eosinophil and lymphocyte counts in cases of milk fever, suggestive of a "stress" response and three animals given 250 units of ACTH recovered, though conventional therapy had been of little benefit. Westermarck (1953) also claimed success with ACTH after failure of calcium therapy. An indication that "exhaustion" of the pituitary-adrenal system may be associated with milk fever came from the experiments of Holcombe (1953). He found a marked decrease in the urinary excretion of reducing steroids in 14 milk fever cases as compared with 20 control animals. But at the present time there seems to be no convincing evidence that adrenal hypofunction is the cause of milk fever rather than the result. A measure of the need for further research into both ketosis and milk fever and their possible interrelationship is forcefully provided by a suggestion of Bomer (1956) that ketosis is due to hypoparathyroidism and can be cured by dihydrotachysterol.

Mastitis remains the commonest lactational disease of cattle and the greatest impediment to milk production. Any new initiative in the treatment of this condition is therefore devoutly to be desired. For this reason the claim of Schipper (1953) deserves consideration. This author reported that in cases of acute and chronic mastitis a clinical cure could be effected simply by stripping out the affected quarters after injection of oxytocin, and he recommended this treatment as an adjunct to antibiotics. There is no doubt that by this device much more inflammatory exudate can be removed than is otherwise possible. The contraction of unaffected alveoli and the dilatation of the lactiferous ducts brought about by oxytocin would certainly loosen clots and express infected material into the cisterns. But Schipper's conclusions were not supported by later experiments in goats (Smith & Pattison, 1954) and cows (Pattison & Smith, 1954). These workers employed bacteriological criteria of therapeutic response in experimentally produced streptoccal mastitis. However, this work does not dispose of the possibility of a therapeutic effect of oxytocin, for in the first place only one oxytocin injection was given to each cow; daily treatment might have yielded different results. Further, in the second part of the experiment, when the response to combined oxytocin and penicillin therapy was compared with that to penicillin alone, all the control animals showed a bacteriological cure. Understandably, oxytocin could not improve on this. The utility of oxytocin in mastitis therapy, therefore, remains an open question, and one that seems to require more extensive investigation.

One of the least understood lactational disorders of farm live-stock is so-called swine agalactia. This widely met condition is undoubtedly responsible for a significant proportion of early litter wastage, but has been the subject of few published clinical descriptions (but see Hogg, 1952) and no experimental reports. The agalactic symptoms may represent primary secretory failure associated with hypoplasia of the udder, or more commonly in multigravid sows a secondary secretory failure following mammary engorgement and inability to eject milk. A sow normally nurses her litter about once an hour, and the rate of milk secretion may be of the order of half-litre per hour. Hence it might be expected that any interference with milk ejection or withdrawal by the piglets would rapidly build up pressure in the alveoli and initiate involutional changes. The efficacy of pituitrin therapy in many cases would be explained by its effect in evacuating the alveoli of milk and preventing back pressure. We might suppose a variety of possible causes for milk ejection failure: pyrexia, emotional stress, hypocalcaemia, or overproduction of milk leading to occlusion of mammary capillaries (*cf.* first section of this paper). But as yet these are mere speculations. One point on therapy, however, can be made with confidence. The physiological dose of oxytocin for normal milk ejection in the sow is certainly less than one unit. In the doses frequently used (1 to 3 c.c., *i.e.* 10 to 30 units) pituitrin, which has equal oxytocin and vasopressin content, would almost certainly have two undesirable effects, *viz.* constriction of the coronary vessels, and constriction of the mammary blood vessels. The latter result is directly antagonistic to milk ejection, and may be one reason why pituitrin treatment sometimes fails to give the expected response. Use of the purified oxytocic extract (pitocin) would be more rational, preferably given by slow intravenous injection in a dose of ½ to 1 c.c. The response, if present, should then occur within about half a minute of the injection, and would be shown either by a sudden facility for manual expression of milk from the teats, or by the behaviour of the sucking piglets as they begin to withdraw milk. Another therapeutic agent for which claims have been made is chorionic gonadotrophin. So far there is no satisfactory suggestion as to its mode of action. It is difficult to see how luteinising hormone could affect milk ejection or secretion, and the possibility that any positive effect may be due to contaminants or incidental factors is not excluded. In an effort to gain some much needed information on the events occurring in the udder of the sow, a biopsy technique has been developed by my colleagues R. F. W. Goodwin and I. A. Silver and myself at the School of Veterinary Medicine, Cambridge. With this technique a study has been started of the histological changes taking place in the mammary gland before, during and after parturition, when milk removal is prevented, and in cases of agalactia. It is hoped that this investigation may lead to a better understanding of lactational function and disorder in this species.

Summary

The rate of milk production of an animal is determined by the number of secretory cells in the mammary glands and by the speed of milk formation in these cells. Growth of the mammary parenchyma from puberty depends upon the co-operative action of pituitary and gonadal hormones. Secretion of milk is controlled by the pituitary, thyroid, adrenal cortex, parathyroids and pancreatic islets but little is known of the site or mode of action of their respective hormones. The milk-ejection reflex is important in maintaining milk secretion by evacuating the alveoli. Its nature and properties are discussed and reference made to the lactational role of suckling or milking in stimulating both lobes of the pituitary gland.

Individual milking characteristics in cows result from differences in the pattern of milk ejection. Effects of management on milk performance are considered with special reference to "double ejection" and emotional inhibition of milk ejection. Of the various hormone treatments devised to induce or enhance lactation pituitary growth hormone appears effective, while lacking the undesirable features of treatment with oestrogens or thyroactive agents.

A number of lactational disorders of farm livestock are considered from the standpoint of pathological physiology. A lot of research has yielded little unequivocal evidence on the essential nature of bovine ketosis or milk fever. Present theories postulating adrenocortical, parathyroid or thyroid dysfunction are discussed. The possible value of oxytocin in mastitis treatment remains to be established. Finally the problem of swine agalactia is briefly considered.

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THE SPEAKER'S INTRODUCTION

Dr. B. A. Cross, presenting the paper, first apologised for what he described as the "somewhat inelegant title of the paper." When it was written four months earlier his aim had been to try to use recent work on lactational physiology to illuminate some of the problems that he thought might beset veterinarians in the field. As the Chairman had pointed out, it was impossible for any one man to have complete competence in such a vast territory and he had had to extend beyond the limits of his own research experience. He therefore hoped that the many experts present would take a charitable view of any shortcomings that might result. With the help of some colour slides Dr. Cross proposed to confine his remarks to one facet only of the total picture—the question of lactation in pigs, and swine agalactia, which was touched on at the very end of his paper. The work illustrated by the slides was in large part due to the labours of his two colleagues, Dr. Goodwin, who was present, and Mr. Silver, who was at that moment

in the Sahara Desert. Dr. Cross then showed the slides which traced the histological changes occurring in the mammary glands of sows in the days immediately preceding and following farrowing. The material was obtained by a biopsy technique which allowed repeated sampling of the same gland in any one sow. Involutional changes following taping the teats to prevent milk removal were illustrated. Biopsies taken in the same way from several cases of agalactia indicated that at least three distinct types of mammary derangement might occur in the syndrome. Dr. Cross expressed the hope, in conclusion, that more experiments of this sort might eventually throw light on the aetiology of some of the presently inscrutable lactational disorders seen in practice.

The Opener

Dr. A. Marr (Sevenoaks), opening the discussion, said that the paper gave an admirable and very clearly presented review of the modern conception of lactational physiology, and Dr. Cross had done a valuable service in presenting, in a concise and succinct form, knowledge which, for most, was not easily acquired. The paper covered an enormous field, and even had he the ability, he could not, in the time at his disposal, hope to comment on more than a mere fraction of it. Therefore, as he had been asked to open the discussion from the point of view of the clinician, he would confine himself to that part which had the most immediate clinical applications—namely, that part dealing with the physiological foundations of lactational disorders, within which compass he would concentrate on bovine ketosis and milk fever. He would attempt to approach those disorders from the clinical aspects which to him seemed to have a bearing on their pathological physiology and rational therapy.

Dr. Cross had confined himself, in dealing with bovine ketosis, to a consideration of the theories of Shaw and his co-workers that ketosis could be considered to be a "disease of adaptation" brought on by the "stress" of parturition. He had given a very fair and balanced appraisal of those theories but Dr. Marr thought it fair to surmise that Dr. Cross regarded them as so far unproven, and he himself, without presumption, concurred. There was, for instance, the assertion that the disease was brought on by the stress of parturition. If that were so, why should the onset of the clinical condition be delayed usually until 7 to 14 days, and frequently until as late as 6 to 8 weeks after calving? If "stress" was a factor, the stress of lactation must be the more important one.

Like Dr. Cross, he found it surprising that a relatively benign condition—in his experience never fatal in its primary form and one which frequently responded to a simple form of therapy—should have such definite and wide-spread *post-mortem* lesions as those described by Shaw and his co-workers. One was entitled to wonder, from the wide variety of the lesions found, whether in fact these were all cases of primary ketosis sacrificed for experimental reasons, as claimed by Shaw, or whether in some the ketonaemia was of a secondary nature. The poor response to glucose therapy quoted by Dr. Cross did not agree with experience in the Sevenoaks practice. That might be because, at Sevenoaks, they used relatively large doses of glucose—16 oz. of glucose monohydrate dissolved in a litre of water and given intravenously. Such dosage might appear to be excessive—it did, in fact, produce a glycosuria after injection—but they had found that nearly all cases of primary ketosis had responded to it, although a proportion had relapsed and had required a second and, more rarely, a third treatment, sometimes supplemented by oral dosing with propylene glycol. Shaw had found that where no response was obtained to cortisone therapy, the ketosis was usually secondary. Dr. Marr made the same claim for glucose therapy as he had found that the majority of cases where there was little response to it were cases where the ketonaemia was secondary to some other condition such as displacement of the abomasum, Johne's disease, metritis, and, more rarely, traumatic reticulitis, but even there some recession of the ketonaemia, as measured by Rothera's test on the milk, usually resulted from treatment. A few cases occurred where there was a poor response to glucose therapy and in which no other disease condition could be diagnosed, and in those there was sometimes a response to ACTH therapy. That could be interpreted as supporting Shaw's views, but it could equally well be that the "stage of exhaustion" of the pituitary was a result of the prolonged illness and not the cause of it.

Dr. Marr said that although he himself had only a limited personal experience of the routine use of ACTH in the treatment of primary ketosis, his colleagues at Sevenoaks had tried it fairly extensively about 3 years previously. They had found that treatment with 200 units was roughly as effective as glucose therapy and, for reasons of economy, they had reverted to glucose. In trying to assess the place of ACTH in general therapeutics, he was reminded of the claim of the Danish-American comedian, Victor Borge, that his grandfather had invented a cure for which there was no disease. (*Laughter.*) He thought that ACTH might well be described as the cure for which there were too many diseases.

He thought it misleading to state, as Shaw was quoted in Dr. Cross's paper as doing, that primary ketosis was "caused" by adreno-cortical insufficiency. That might be the underlying mechanism involved in the genesis of the disease—and Shaw and his colleagues deserved full credit for their investigations into it—but surely it could not be said to be the cause. To say that might appear to be quibbling, but it was important to make the distinction as, from the practical point of view, the elucidation of the ketosis problem would await investigation of the nutritional factors which were undoubtedly involved in the aetiology. In that connexion he had been a little disappointed that Dr. Cross did not include some reference to any of the work carried out on the inter-relationship of ketosis and rumen digestion. Dr. Cross had had to be selective—indeed, a whole paper could be devoted to that subject alone—and he might be able to tell them something about it in his reply.

It was with some trepidation that Dr. Marr turned to milk fever, as he was loath to add his name to the list of those theorists who had been so often wrong and those blushes Dr. Cross had been anxious to spare. In milk fever even more than in ketosis, they were presented with a clinical syndrome where a dramatic response was obtained to a simple and relatively short-acting remedy, though one had to beware of arguing from that that the physiological foundation must therefore be of a simple nature. Nevertheless, he agreed with Dr. Cross that they must be careful not to place causal attributes on evidence which might indicate multi-glandular dysfunction, as had been postulated by some, but which might equally be resultant in nature. He still adhered to the opinion (Marr, 1952) that it was difficult to visualise the nature of a multi-glandular dysfunction which was of such a temporary character and which was readily rectified by a treatment essentially replacement in effect.

Two aspects of calcium metabolism which had recently been investigated by Comar and his associates in the Institute of Nuclear Studies at Oak Ridge, Tennessee, seemed to him to have a considerable bearing on the problem of milk fever. First, Hansard, Comar, and Davis (1954) had shown that there was a marked decrease with advancing age in the rate of exchange of calcium ions between blood and bone—decreasing from nearly 100 per cent. of the total blood calcium per minute in young cattle to little more than a quarter of that in aged cattle. Secondly, Visek, Monroe, Swanson, and Comar (1953) had demonstrated, among other interesting factors, a similar decrease with advancing years in the efficiency of intestinal absorption of calcium. Such evidence went far towards explaining the age incidence of milk fever and the inability of the older cow sufficiently rapidly to counteract the drain of calcium into the colostrum, which was the immediate cause of the hypocalcaemia.

The investigation of variations in the rate of calcium absorption from the gut he found of particular interest, as he had observed that so-called atypical hypocalcaemias—occurring away from the parturient period and which were relatively so common in the Jersey breed—were very often related to alimentary disturbances. That hypocalcaemia could result from overfeeding with concentrated feeding-

stuffs—cereals in particular—had been known for years. Such cases were fairly often seen in individual animals, but Dr. Marr had recently encountered an outbreak of scouring in a Jersey herd due, apparently, to the accidental feeding in the concentrate ration of excessive amounts of wheat. Seven animals—100 per cent. of the recent calvers in the herd—were affected. The condition was accompanied by hypocalcaemia, and it was interesting to note that 5 of the animals which were third calvers or older showed an average serum calcium concentration of 4.5 mg. per cent., while the other 2, which were first calvers, had serum calcium levels of 9.6 and 8.9 mg. per cent. A similar outbreak in recent calvers was seen in the same herd while it was affected with the condition of " winter scour."

Dr. Marr added that he had also seen individual cases of hypocalcaemia associated with definite alimentary disturbance. Thus, he had had 2 cases of displacement of the abomasum, 2 of perforating peptic ulceration of the abomasum, one of tumour formation in the terminal portion of the small intestine, and one case of lipomatosis interfering with the pyloric outlet. All had occurred at peak lactation and in all cases the clinical syndrome was ushered in by an attack of hypocalcaemia confirmed by blood analysis. Most were cows of the Jersey breed. His guess at the inference to be drawn from those cases was that dairy cows at peak lactation—and particularly those of the Jersey breed—were in a precarious calcium balance and very dependent for the maintenance of a normal serum calcium concentration on the constant assimilation of calcium from the gut. Anything which interfered with that assimilation—even for a short time—might precipitate a clinical attack of hypocalcaemia.

Dr. Cross had drawn attention to the work of Boda on the effect of the feeding of a low-calcium high-phosphorus diet in late pregnancy in reducing the incidence of milk fever, and to the converse experiments of Ender and his co-workers. Dr. Cross had pointed out the extremely interesting theoretical implications of those experiments and their possible bearing on the rôle of the para-thyroids in the disease. At first sight, Boda's work might seem to offer an attractive prospect of providing a practical method of prevention of milk fever, but the difficulties attendant on the provision of such a ration, and the possible harmful side effects which might result, seemed to preclude its application at present. Boda's findings might, however, explain why some herds suffered a much higher incidence of the disease than did others.

Another possible method of prevention, based on the work of Hibbs and his co-workers and entailing the feeding of massive doses of vitamin D for 7 days before the expected calving date, had recently received considerable prominence in the agricultural press. A recent small-scale trial of the method, carried out in collaboration with Dr. Ruth Allcroft of Weybridge, in 2 Jersey herds with a high incidence of milk fever had produced the following results.

Six untreated control animals all developed milk fever—a rather better result than that usually obtained. In 5 out of a total of 8 animals treated the administration of the vitamin D preparation had to be suspended after 3 or 4 days, due to its unpalatability when mixed with the concentrate ration. Consequently, in those cases there was a gap of 3 or 4 days between the end of vitamin D feeding and calving. Two of the 5 animals developed milk fever. The 3 remaining animals had the full seven-day course and none of them developed the disease. All had normal levels of serum calcium at calving, but 2 of them developed hypocalcaemia, one 5 days and the other 14 days after calving. Such data were, of course, too limited to warrant the drawing of firm conclusions, but they tended to underline the findings of Hibbs and Pounden (1956) that little protection could be expected until vitamin D had been fed for at least 3 days and that protection could not be expected to last longer than one or two days after vitamin D feeding had stopped.

Dr. Marr thought that, in general, it was fair to say that the narrow limits of protection afforded by vitamin D feeding, and the difficulty of forecasting accurately the exact date of calving, coupled with the real dangers attendant on too-prolonged feeding of the vitamin, made the method difficult to apply at present, although it might become feasible in herds which suffered a high incidence of the condition. The comparatively low incidence of the condition on the average farm and the generally successful results obtained from calcium therapy forced him to accept the paradox that at present, cure was better than prevention of the disease.

Dr. Cross had mentioned pyrexia and hypocalcaemia as possible causes of failure of milk ejection in sows. Dr. Marr agreed with Hogg that the condition of hypocalcaemia rarely, if ever, occurred in sows, and he would like to hear what Dr. Cross had to say in that connexion. He also agreed with Hogg that pyrexia was more frequently associated with failure in milk secretion than with failure in milk ejection.

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The General Discussion

Dr. J. L. Linzell (Babraham): " I agree that the mammary myoepithelial or basket cells are very difficult to stain. Some years ago I did stain them, however, in the same way as Richardson, that is by accident when staining mammary nerve endings with silver. I spent some time in a vain attempt to get the method to work every time but now feel that the alkaline phosphatase method is very much less capricious.

" Once these cells are stained their abundance is most impressive, not only the stellate cells around the alveoli, but also the aciculate variety along the outside of the ducts. Although it is true that no one has seen one contract it is possible to see the contraction of the alveoli in the living mammary gland of small animals under anaesthesia. Not only do the posterior pituitary hormones cause the squeezing of the milk from the alveoli into the ducts, but so do other drugs that cause the contraction of smooth muscle, *e.g.* acetyl-choline and other choline esters, pilocarpine, histamine, and barium chloride. If it is admitted that it is unlikely that the secretory cells themselves, the connective tissue, or the blood vessels could cause this active process, it can only be the myoepithelial cells, which are so ideally situated for the purpose.

" The origin of these cells is of great theoretical interest. It is salutary to remember that they were first described by Henle and Kölliker in 1850, and that the German histologists of the last century believed, not only that myoepithelial cells were contactile, but were derived from the ectoderm. Since they were right in the first case I feel that we should again attempt to test their second belief with modern methods."

Dr. Goodwin (Cambridge) explained that the mammary biopsy specimens, of which sections had been shown by Dr. Cross, were obtained with the trocar and cannular equipment made by Arnold and Sons for taking liver biopsies at Weybridge. The instrument was driven into the mammary gland very sharply by striking the trocar head with a wooden mallet, and a thin worm of mammary tissue about 2 inches long was withdrawn. The success of the procedure depended very largely on the way in which the trocar was held and struck. Once the technique had been mastered, the time between tethering and releasing the sow after sampling was about 10 minutes. As many as 15 biopsies had been taken from only two glands of an animal over a period of 18 days without any obvious effect on appetite or lactation. Dr. Goodwin was now using the technique to obtain specimens for bacteriological examination.

Mr. K. N. Burns (Weybridge) " Dr. Marr has mentioned massive-dose vitamin D administration in connexion with the control of milk fever, and has pointed out that inappetence may follow the mixing of vitamin D with the concentrate ration. We have given the same dosage of vitamin D to a number of cows by daily drench, and in these

cases there has been no evidence of inappetence. In those animals where it was possible to compare milk yield with the previous lactation no lowering of yield occurred. Blood calcium and inorganic phosphate values remained within the normal range at parturition."

Mr. J. B. White (Salisbury) said he would like to thank Dr. Marr and Professor Robertson for reminding them of the part played by digestive disturbance in the causation of acetonaemia.

He thought that acetonaemia would result in almost any circumstance where milk output exceeded food intake in the heavy milking cow; and that the different lines of treatment in general use arose simply because of the widely different causes of digestive upset which gave rise to acetonaemia as it occurred from district to district.

In Wiltshire glycerine gave a high measure of success, but he would like to mention that in the cases where response was unsatisfactory they found that a cessation of milking would invariably effect a cure and that the cow would still return to a good milk yield where appetite was recovered.

The Reply

Dr. Cross, replying to the various points raised in the discussion, said that though at the time it had seemed reasonable to take such a wide brief, the large number of searching questions directed at him now made it clear that to do so had been a tactical error. Fortunately in many cases one speaker had answered another. He was very grateful to Dr. Marr for a brilliant opening address which seemed to put the clinician's problems very neatly. Dr. Shaw had come under heavy fire from a number of speakers. There was one point to make in his defence, however, concerning Dr. Marr's question about the ketosis symptoms appearing so long after the " stress " of parturition. This delayed onset of symptoms was consistent with the adrenal insufficiency theory according to which the ketosis occurred in the " exhaustion phase " of the so-called General Adaptation Syndrome, not in the initial phases. Dr. Marr favoured the view that many cases of bovine ketosis were secondary to other conditions or factors. Dr. Shaw would probably not deny this. His group had published some evidence that primary ketosis was distinguishable from one form of secondary ketosis, *i.e.* the nutritional variety, by the higher ketonaemic levels found in the former. Dr. Cross believed that one of the big weaknesses of Shaw's theory arose from the fact that he defined primary ketosis as an adrenal insufficiency on the basis of a favourable response to ACTH or cortisone. When cases did not respond they were said not to be primary ketosis. By this simple device he could claim exceedingly good results for adrenocortical therapy in the condition, but there seemed to be a certain circularity of argument here.

Dr. Cross had tried to make clear in his paper that his remarks on swine agalactia were only tentative. He had not wished to imply that he had evidence that hypocalcaemia actually occurred in association with agalactia. For a heifer he thought the right intravenous dose of oxytocin would be about one international unit, *i.e.* one-tenth of a c.c., of commercial Pitocin. If given intramuscularly a larger dose would be required. He was glad Dr. Blackburn now felt able to accept the existence of myoepithelial cells and grateful for his observations on the fat-laden cells in the mammary glands of cows when lactation was suppressed. Dr. Linzell, who had contributed greatly to our knowledge of mammary myoepithelium, had made some very helpful remarks on this topic. With regard to the problem of staining the tissue, the work of Mr. I. A. Silver had shown that Gomori's alkaline phosphatase method was entirely reliable. Dr. Goodwin had covered the biopsy technique in detail. There was one thing that might perhaps be added concerning haemorrhage. Small amounts of haemorrhage occasionally occurred during the taking of biopsies. They were, however, readily controllable and did not interfere with the interpretation of the biopsy.

Dr. Cross had found very interesting, suggestions by several participants in the discussion, *e.g.* Mr. White, that suppressing lactation seemed to act effectively in some conditions other than milk fever. There were many physiological repercussions of the build-up of intramammary tension which seemed deserving of further study in connexion with such therapeutic experiences.

The Treatment of Fractures in Farm Animals

BY

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Introduction

DURING the last decade great advances have been made in the treatment of fractures in the smaller domestic animals. This has been due, in no small measure, to the introduction of the antibiotics, improved anaesthetic techniques, a better understanding of the reaction of tissues to metals, and the increasing availability of X-ray facilities to the profession. These advances have enabled open reduction and fixation of fractures to be practised with confidence and safety.

The treatment of fractures is based on reduction, alignment and immobilisation of the part, while maximum use of the limb should be permitted to prevent muscle atrophy and assist healing. The most important factor, without doubt, is effective immobilisation. To this end no one method can satisfy all requirements and so each case has to be considered on its individual merits and, in the light of experience and with the facilities available, the most suitable method or combination of methods adopted. The application of the principles of fracture treatment naturally varies with the type and age of the animal concerned. The farm animals, on account of their size, present numerous difficulties. Special attention has been given to these problems, and during the last 4 years 17 bovine animals, 3 sheep and 5 pigs have been accepted for treatment. Details of the individual cases and of the methods employed are set out in the attached summary of case histories.

Radiography

For the satisfactory treatment of fractures X-ray facilities are essential. It is necessary to know the exact position and type of fracture, the degree and extent of the displacement, and whether or not there are added complications such as the involvement of a joint. It is not possible by clinical examination alone to assess these factors to the nicety that is required to determine the most satisfactory method of treatment to adopt. Excessive manipulation of the fracture site, especially if performed under general anaesthesia in the hope of making a more accurate and precise diagnosis, invariably results in disappointment and additional injury to the already traumatised tissues and structures. To obtain an accurate picture of the injury it is necessary to have radiographs taken in at least two planes. In addition to their value in making an accurate diagnosis and prognosis, radiographs can usefully be employed to check the result of operative procedures and manipulations, and to follow the course of fracture repair.

Reduction and Alignment

The chief difficulty in effecting reduction and alignment is to overcome the local muscle spasm at the fracture site. This is chiefly due to local tissue irritation and therefore cannot be directly controlled either by a general anaesthetic or one combined with a muscle relaxant drug. However, to a great extent, it may be overcome by applying continuous and prolonged traction which produces muscle fatigue. In those cases in which there is displacement and overriding of the fractured ends, reduction is practically impossible without resorting to mechanical measures and direct manipulation of the bone ends, following their exposure.

In the smaller domestic animals a Gordon Extender or some modification of it is satisfactory for producing muscle fatigue by continual and prolonged traction. In the farm animals more force is required so a block and tackle is indispensable for this purpose. In many cases with gross overriding, uninterrupted and often increasing traction has to be applied for 20 to 30 minutes before adequate relaxation is obtained. In cases when adequate reduction cannot be obtained by traction of the limb (see Fig. 1), the question of applying direct traction to the bone ends, using tration tongs or a transfixing Steinman pin, should be considered.

To reduce and align an overriding fracture effectively in the farm animals it is necessary to combine continual traction with open reduction. Traction should be commenced immediately the animal is anaesthetised and positioned and a satisfactory degree of muscle fatigue should have developed by the time the fracture site is exposed. Traction, exposure of the fracture site and freeing of the bone ends by no means ensures an easy reduction and alignment. Invariably it is necessary to apply bone-holding forceps and very considerable force and ingenuity before the bone ends can be manoeuvred back into position. In some cases, to facilitate reduction and to ensure a good fit, it is necessary to trim the bone ends. (See Fig. 2 (a) and (b).) This results in a degree of shortening of the limb when healing is complete, but provided it is performed within reasonable limits does not seriously interfere with the locomotor efficiency of the animal.

Immobilisation

Immediately following a fracture Nature attempts immobilisation by local muscle spasm and later, as healing progresses by strutting the fractured ends with callus. The more efficient the immobilisation, the more rapid the healing, together with less callus formation and risk of a non-union. Many methods can be employed to immobilise fractures. Each method has its uses and for purposes of discussion they may be divided into the methods of external and internal fixation.

External Fixation

Plaster casts and splints of numerous varieties can all be used to advantage. In fact, for those frac-

CATTLE

Breed	Age	Sex	Clinical examination	Type of fracture	Treatment	Remarks
1. Guernsey	2 days	F	Unable to stand. Obvious fracture midshaft tibia	Transverse mid-shaft fracture of tibia with over-riding	Open reduction and fixation. Stainless steel Sherman plate and screws.	Died 2 days post-operation. *Post-mortem* revealed crushed spleen and kidneys.
2. Devon	3 days	M	Carried left front leg. Swelling and oedema from elbow to knee. Abnormal movement and crepitus above knee.	Transverse fracture lower third radius and ulna with over-riding.	Open reduction and fixation with an Eggers type stainless steel plate and screws. Reinforced with a plaster cast from elbow to foot.	Discharged 55 days post-operation. Limb crooked but calf very active.
3. Friesian	10 M	F	Carried right hind leg. Took a little weight on it when at rest. Local swelling and abnormal movement lower end of femur.	Epiphyseal separation lower end of femur. Shaft overriding condyles by 4 to 5 inches.	Fracture site exposed but unable to effect reduction.	Destroyed.
4. Jersey	13 M	F	Carried limb. Punctured wound on the medial aspect of limb just below knee. Abnormal movement and crepitus.	A compound transverse fracture of the upper end of metacarpal bone with medial displacement of shaft. No overriding.	Following debridement the limb was supported in a plaster cast which extended from the elbow to the foot. This was reinforced by incorporating in it an iron bar 12 × 1 × ¼ inches. Plaster removed after 3 weeks.	Heifer took weight and used the limb from 3rd week. Discharged from hospital 30 days post-operation. Using limb but slight contracture of fetlock joint. Small exostosis upper end of metacarpus. Final result entirely satisfactory.
5. Shorthorn	2 days	F	Marked swelling from elbow to knee. Abnormal movement and crepitus mid forearm.	Oblique fracture lower third radius and ulna. Upper fragment overriding 1½ to 2 inches.	Open reduction and fixation using a Venable type stainless steel plate and screws.	Calf used limb 24 hours post-operation. 7 weeks later satisfactory callus formation and calf using leg normally. No deformity.
6. Friesian	3 days	F	Unwilling to stand unless supported. Abnormal movement just above hock joint.	Oblique fracture lower third tibia with overriding 2 to 3 inches.	Open reduction and fixation using a Venable type stainless steel plate and screws.	Calf using limb 48 hours post-operation. 8 weeks later satisfactory callus formation and calf using limb normally.
7. Shorthorn	2½ years	F	Unable to take weight. Abnormal movement and crepitus below knee.	Comminuted fracture upper end of right metacarpal bone. Little displacement.	Immobilised in a plaster cast from elbow to foot which was reinforced by incorporating in it an iron bar 10 × 2 × ¼ inches.	After 4 weeks cast removed. Callus formation satisfactory but limb crooked. Sold for beef 5 months later.
8. Hereford	9 M	M	Unable to extend right foreleg. Elbow dropped. Fetlock flexed and claw dragged.	Oblique fracture mid-shaft humerus with fragment of bone detached.	Fracture immobilised with a stainless steel intramedullary pin ⅛ inch in diameter.	Post-operation a slight extensor paralysis persisted for 3 months. One year post-operation bullock absolutely sound.
9. Shorthorn	6 M	M	Recumbent. Abnormal movement and crepitus upper end of tibia.	Transverse and impacted fracture upper end of tibia. Little displacement.	Fracture immobilised with a ¾-inch stainless steel intramedullary pin.	Destroyed 3 days post-operation. Unable to stand due to rupture of pectoral muscles.

Breed	Age	Sex	Clinical examination	Type of fracture	Treatment	Remarks
10. Friesian	2 years	F	Recumbent. Compound fracture lower end of tibia.	Compound and comminuted fracture with gross displacement.	Nil	Destroyed
11. Lincoln Red	9 M	M	Standing on 3 legs. Abnormal movement mid-tibia region.	Comminuted fracture mid-shaft of tibia.	Open reduction and fixation with a Venable type stainless steel plate and screws.	Uneventful and satisfactory recovery.
12. Shorthorn	3 days	F	Swelling and abnormal movement just above the fetlock joint.	Transverse fracture of the lower end of the right metatarsal bone with lateral displacement.	Fracture reduced and immobilised in a plaster cast from just below the hock joint to the foot.	Plaster removed after 1 month. Callus formation satisfactory and the calf was taking weight and using the limb. Final result entirely satisfactory.
13. Jersey	3 days	F	Abnormal movement and crepitus lower end of humerus.	Fracture of medial condyle of humerus with very slight displacement.	Limb immobilised for 4 weeks in a plaster cast from above elbow to fetlock.	Uneventful and satisfactory recovery.
14. Jersey	9 years	F	Standing on 3 legs. Swelling forearm and knee. Abnormal movement and crepitus above knee.	Comminuted fracture lower end of radius and ulna.	Open reduction and fixation. Venable type stainless steel plate and screws. Reinforced with a plaster cast from elbow to foot.	Struggled 2 days post-operation. Plate bent and screws broken. Destroyed.
15. Jersey	10 M	F	Standing on 3 legs. Abnormal movement and crepitus mid-humerus region.	Comminuted fracture shaft of humerus with distal fragment impacted.	No immobilisation attempted. Put into loose-box.	Satisfactory healing after 4 months.
16. Friesian	16 M	M	Deformity and swelling fetlock region.	Comminuted fracture lower end of metacarpus with gross displacement.	Nil.	Destroyed.
17. Guernsey	11 M	M	Unable to take weight. Leg swollen from hip to hock. Crepitus lower end of femur.	Fracture lower end of femur with extensive overriding.	Nil.	Destroyed.

SHEEP

Breed	Age	Sex	Clinical examination	Type of fracture	Treatment	Remarks
1. Dorset Horn	9 M	M(N)	Carried leg. Small painful swelling just below the knee.	Transverse fracture upper end of metacarpal bone. Very little displacement.	Immobilised in a plaster cast for 3 weeks.	Uneventful and satisfactory recovery.
2. X-bred	2 years	F	Carrying left hind leg. Abnormal movement and crepitus mid-tarsal region.	Oblique fracture middle and lower third tibia with overriding and angulation. A detached piece of bone 1 × ½ inch.	Open reduction and fixation with a Burns type stainless steel plate and screws.	24 hours after operation bent plate 20°. Reoperated using a Venable type plate. Final result entirely satisfactory.
3. Dorset Horn	8 weeks	M	Compound fracture left metatarsal bone.	Oblique fracture middle and lower third left metatarsal bone.	Debridement followed by reduction and immobilisation in a plaster cast.	Plaster removed after 3 weeks. Skin wound had healed. Satisfactory callus formation present. Uneventful and satisfactory recovery.

PIGS

Breed	Age	Sex	Clinical examination	Type of fracture	Treatment	Remarks
1. Large Black	3 years	F	Carried left hind leg. Swelling above hock joint and abnormal movement lower third of tibia.	Oblique fracture lower third tibia with overriding.	Open reduction and fixation with a Sherman type stainless steel plate and screws.	Uneventful recovery. Walking well after 5 weeks.
2. Large Black	2½ years	F	Carried left hind leg. Abnormal movement lower third of femur.	Oblique fracture lower third of femur with marked overriding.	Open reduction and fixation with a Venable type stainless steel plate and screws.	Uneventful and satisfactory recovery.
3. Essex	3 years	F	Limb held flexed. Abnormal movement and swelling mid-thigh.	Oblique fracture mid-shaft femur with overriding.	Open reduction and fixation with a Venable type stainless steel plate and screws.	Uneventful and satisfactory recovery.
4. Landrace	3 years	M	Carried left hind leg. Swelling and abnormal movement mid-thigh.	Oblique mid-shaft fracture of femur.	Open reduction and fixation with a Venable type plate and screws.	Progress slow due to muscle abscess. Final result entirely satisfactory.
5. Landrace	10 M	F	Carried left hind leg. Abnormal movement mid-thigh.	Transverse fracture shaft of femur with overriding.	Open reduction and fixation using a Venable type stainless steel plate and screws.	Uneventful and satisfactory recovery.

tures below midshaft radius and ulna and tibia in which there is no displacement or overriding, and only alignment is required, they are invariably the most satisfactory form of treatment and are all that is needed. In general the plaster-cast method is the most useful and adaptable form of external fixation. In farm animals, depending on their individual size, the cast must be at least ¼ to 1 inch thick. In many cases the plaster cast will require to be reinforced. This may be done by incorporating in the cast an iron bar, 1 to 2 inches in width and ¼ inch thick, cut to the required length and bent to conform to the contour of the limb. As a rule plaster casts and the like are of little use for immobilising fractures above either the elbow or hock joints as, due to the shape of the limb and muscle mass, they provide little support. For plaster casts to produce the most effective immobilisation they must be moulded as close to the limb as possible and immobilise the joints immediately proximal and distal to the fracture site. (See Fig. 3.) It is customary to leave a plaster cast on in the first instance, for 3 to 4 weeks. In many cases, in which there is considerable local swelling, they become loose after 7 to 10 days and must be removed and reapplied.

Of recent years both the Stader and Kirschner-Ehmer splinting apparatus have received enthusiastic support as methods of external fixation. They came into vogue when the increasing use of radiography demonstrated the poor results often obtained by the conservative methods of treatment (see Fig. 4 (a)), and before the advent of the antibiotics which resulted in a renewed interest and adoption of internal fixation methods. Their use in farm animals is limited as the apparatus is not well tolerated, does not effect rigid immobilisation and, in spite of the wide range of antibiotics, there is the ever-present danger of osteomyelitis by a spread of infection from the skin around the pins.

Internal Fixation

Wire, screws, plates and screws and intramedullary pins are the most common agents employed for the internal fixation of fractures. Without doubt, the most rigid immobilisation at the fracture site can be obtained by the correct use of a plate and screws. To prevent the plate becoming loose and moving out of alignment or the distal fragment rotating, at least 2 screws must be inserted on either side of the line of fracture, and to ensure that the screws do not become loose they must penetrate both cortices. (See Fig. 8 (b).)

The strains and stresses imposed on both plate and screws when the animal either struggles or begins to take weight following operation are tremendous. Plates are bent and twisted and screws snapped. (See Figs. 4 and 5.) For this reason, when selecting a plate, one should err on the side of greater thickness, width, and where possible length, than one would ordinarily consider suitable. There are numerous types of orthopaedic plates. The strongest and most suitable for general farm animal orthopaedics is the Venable type plate which should be at least ⅛ inch thick and ⅝ inch wide. Occasionally it is found that the screw holes are not conveniently placed for dealing with a particular fracture. In these cases it is necessary to resort to an Eggers (see Fig. 9 (b)) plate in which the individual crew holes are replaced by a slot. This permits a choice of position when placing screws but this advantage is only obtained at the expense of strength. The standard orthopaedic screw is the Sherman type. It is made in lengths varying from ½ inch to 3 inches and all are of a standard diameter, 9/64 inch. These

screws have been employed successfully but in many cases a thicker screw is desirable. A Sherman screw 5/32 inch in diameter and varying in length from ½ inch to 2 inches can be obtained but must be used with plates in which the screw holes have been suitably modified to ensure an accurate fit between the neck of the screw and the plate. Plates and screws have been successfully employed to immobilise fractures of the radius and ulna and tibia in cattle, fracture of the tibia in a sheep, and fractures of the femur and tibia in pigs.

Immobilisation using intramedullary pins is a popular method of treating a variety of fractures. To effect satisfactory immobilisation they must fit firmly into the medullary cavity but, even so, they do not control rotation completely, especially if the fracture is towards the distal extremity of the bone. In theory intramedullary pins should prove most useful for immobilising fractures of those long bones which have a straight and wide medullary cavity, for example, the femur. The author has not had an opportunity to employ intramedullary fixation for the treatment of fractures of the femur in either cattle or sheep, but a colleague who has used this method in cattle stated that a stainless steel rod, ½ inch diameter, was required. Due to its weight it forced its way through the distal extremity of the femur and protruded through the skin in the stifle region.

The pig has a very short femur, with a very wide medullary cavity, which is deeply embedded in the thigh muscles. Therefore, a very short and very thick intramedullary pin is required which, coupled with the depth at which the femur is situated, does not make this method a practical proposition for dealing with fractures of the shaft of this bone in the pig.

The author has used a stainless-steel rod, ½ inch in diameter, to immobilise successfully the fractured humerus of a 9-month-old bullock. (See Fig. 6.) In this case the rod was driven up the proximal fragment, from the fracture site, to protrude on the medial aspect of the lateral tuberosity. After reduction and alignment it was driven back down the medullary cavity of the distal fragment to within ½ inch of the coronoid fossa. The protruding portion at the proximal end was then sawn off level with the top of the lateral tuberosity. Very great force is required to drive a pin of this diameter through the head of the humerus. This may be facilitated by drilling a hole, of considerably smaller diameter, to take the pin.

Materials Used for Internal Fixation

The two most popular metals employed for internal fixation are vitallium* and stainless steel. Vitallium is a chrome-cobalt-molybdenum alloy which is very inert in tissues, possesses satisfactory physical properties but is expensive. There are numerous grades of stainless steel and the tissue reaction they provoke varies considerably. The most suitable stainless steel is one containing 18 parts chromium, 8 parts nickel and from 2 to 3 per cent. molybdenum. This stainless steel is referred to as being an 18/8 SMo steel and for all practical purposes is as inert in tissues as vitallium, has as satisfactory physical properties and the added advantage of being cheaper.

It is most important when using stainless steel materials to know their exact composition so that plates and screws of a different composition are not inserted into the same animal. If this should happen, then as a result of electrolysis, corrosion of the steel and bone necrosis occurs. This in turn results in loose screws and plates and failure of immobilisation.

The problem of corrosion and bone necrosis does not end with the selection of suitable metals. Care has to be taken to ensure that their corrosion resistance is not damaged by handling. The surface of stainless steel, for example, is protected by a film of oxide which is insoluble in the surrounding body tissues. If this protective layer is damaged corrosion will occur. This hazard may be reduced by not bending plates unnecessarily, and by ensuring that surfaces are not scratched by rough handling with instruments, etc. Another point to be considered is metallic transfer. When two metals are brought together and separated small particles of one are plucked out and remain adherent to the surface of the other. Thus transfer may occur from screwdriver to screw head, especially if slipping occurs or from the drill to the edge of the screw hole in the plate if it touches during drilling. This transfer of a dissimilar metal creates an electric cell and results in corrosion.

Exposure of Fracture Sites

Adequate exposure of the fracture site presents little difficulty provided anaesthesia is satisfactory, the limb suitably positioned and a degree of muscle relaxation present. As far as possible exposure should be made along the lines of cleavage between muscle planes thus reducing tissue damage to a minimum and avoiding the majority of the nerves and blood vessels. In many cases the normal anatomical arrangement will be considerably altered due to displacement of the fractured ends, local muscle contraction and mutilated and torn tissues. This greatly adds to the difficulty of making a rapid and trauma free exposure.

Femur

The shaft and lower end of the femur may best be approached from the lateral aspect of the limb. Exposure is obtained *via* a skin incision, extending practically the whole length of the femur, along the line joining the great trochanter and the lower and anterior aspect of the stifle joint. Next the fascia lata is incised, the whole length of the incision along its junction with the biceps femoris. This exposes the muscle bellies of the biceps femoris and vastus lateralis which are separated by blunt dissection to expose the lateral shaft of the femur. This exposure has proved quite satisfactory for cattle, but in the pig the biceps femoris is inserted towards the anterior aspect of the shaft and has to be incised across its fibres before exposure is obtained.

* Vitallium—Vinertia is the British equivalent which is manufactured by the Deloro-Stellite Co. and distributed by the London Splint Company.

Tibia

The medial surface of the tibia is wholly subcutaneous and can therefore be satisfactorily approached from this aspect. The bone may be exposed either by a skin incision along the midline of the medial aspect or by deflecting a flap of skin posteriorly from the anterior border of the medial aspect. This latter method is employed when the fracture is immobilised with a plate and screws and it is not considered good practice for them to lie immediately beneath the suture line. When operating on tibial fractures an intense reaction in the subcutaneous tissues has been observed. Within 48 hours they have become thickened and developed into a haemorrhagic homogeneous mass a ¼ to ½ inch thick. This has to be incised to expose the fracture, and at the termination of the operation can be sutured over the plate to prevent it lying immediately subcutaneous and in contact with the suture line.

Humerus

The shaft of the humerus is approached from the antero-lateral aspect *via* a skin incision along the line joining the lateral tuberosity and the lateral epicondyle. The lateral head of the triceps and the brachialis are then located, and by separating them along their lines of cleavage the shaft of the humerus is exposed.

Radius and Ulna

The animal is restrained in ventral recumbency with the limb pulled well forward and the head deviated to one side. The radius is approached from the anterior aspect *via* a midline skin incision from just below the elbow to a little above the knee. The line of cleavage to be adopted will depend on the displacement and position of the fractured bone. As a rule the most suitable line of cleavage is anteromedially between the extensor carpi radialis and the flexor carpi radialis, but on occasions the anterolateral approach between the extensor carpi radialis and the extensor digiti tertii will be found more suitable.

Closure and Post-operative Complications

It is the author's practice to coapt all divided tissues, as far as possible, back into their normal anatomical positions using interrupted chromic catgut sutures. The size selected should be as fine as possible consistent with the strength required. The skin is closed either with simple interrupted or mattress sutures, of monofilament nylon, depending on the degree of tension present. The skin wound is then protected by oversewing a gauze pad unless the internal fixation methods are to be further supported with a plaster cast. In this case the wound is protected with Vaseline gauze impregnated with penicillin.

The post-operative complications encountered have been varied. One case of local wound sepsis in a pig rapidly responded following surgical drainage. In a ewe a bent plate (used for immobilising a fractured tibia) (see Fig. 4 (b)) necessitated reoperating and applying a stronger plate. Complete disruption was experienced of plate and screws used in the treatment of a fractured radius and ulna of a 9-year-old Jersey cow. (See Fig. 5 (b).) This occurred in spite of additional external support in the form of a ¼-inch-thick plaster cast and necessitated the destruction of the cow. Two cases occurred of inadequate immobilisation at the fracture site. The stresses of weight bearing could not be sustained, and in consequence, although healing occurred, the limb became crooked. (See Fig. 7.) Muscle atrophy of the affected limb was a common feature and was often associated with a degree of contracture of the knee and fetlock joints. These symptoms were soon alleviated once the animal began to take weight and use the limb.

Time for Operation

Open reduction and fixation of fractures should not be regarded as emergency operations. The most important consideration immediately following a fracture is to prevent further local tissue damage and to control shock. In many fractures, such as those of the femur and humerus, a degree of local immobilisation results from local muscle spasm but this does not hold good for fractures of the tibia and radius and ulna. In such cases it is necessary to immobilise the fracture temporarily with some simple form of external fixation, such as a splint or plaster cast. After 36 to 72 hours the animal will have recovered from the shock of the accident and be a more satisfactory anaesthetic risk. Also, the local tissue swelling will have subsided and the haemorrhage at the fracture site organised, thus facilitating operative procedures. Invariably this lapse of time is required for the preoperative preparation of the animal and to reduce the surgical risk.

Use of Antibiotics

In spite of aseptic operative techniques and the use of inert metals, open reduction and fixation of fractures in the farm animals would not be an accepted routine procedure without the antibiotics and sulpha drug preparations. For routine administration penicillin is still found to be the antibiotic of choice. It is the author's practice to give a 5-day course commencing the day prior to operation. In addition, the exposed tissues are insufflated with penicillin sulphathiazole powder immediately prior to closure. Care should be taken not to apply excessive quantities of these preparations as they are slowly absorbed and their mere mass constitutes a foreign body and may provoke considerable local tissue reaction.

Removal of Internal Appliances

The progress of fracture healing should be checked periodically by radiological examination. Plates and screws must remain *in situ* until satisfactory union is established. If at this stage there is no radiological evidence of bone rarefaction or necrosis they are unlikely to result in any adverse tissue reactions and may be left in permanently. If it is decided to remove a plate and screws then they should not be left

FIG. 1.—Case No. 3. Friesian heifer aged 10 months. Fracture lower end of femur with shaft over-riding condyles by 4 to 5 inches. Unable to effect reduction in spite of direct traction on the bone ends.

FIG. 2(a).—Case No. 3. Essex sow aged 3 years. Oblique fracture mid-shaft of femur with over-riding.

FIG. 2(b).—Note bone ends trimmed to ensure a good fit and fracture immobilised with a Venable type plate and screws.

FIG. 3.—Case No. 3. Dorset Horn ram lamb aged 8 weeks. Oblique fracture lower third metatarsal bone. Note poor reduction by closed method, distance of cast from limb and extent of callus formation after 3 weeks. Satisfactory immobilisation obtained because the joints proximal and distal to the fracture site were included in the plaster cast.

FIG. 4(a). Case No. 2. X-bred ewe aged 2 years. Comminuted fracture mid-shaft tibia.

FIG. 4(b).—Burns type plate bent, 24 hours post operation, when the ewe began to use the limb.

FIG. 5(a).—Case No. 14. Jersey cow aged 9 years. Comminuted fracture lower end of radius and ulna. Accurately reduced and immobilised with an ¼-inch thick Venable type plate and screws.

FIG. 6.—Case No. 8. Hereford steer aged 9 months. Comminuted oblique fracture mid-shaft humerus. Satisfactory immobilisation obtained with a stainless steel pin ½ inch in diameter.

FIG. 7(b).—Fixation with an Eggers type plate and screws. Satisfactory reduction and alignment but plate does not conform to the contour of the bone and only 1 screw in the distal fragment.

FIG. 5(b).—Plate twisted and bent and screws broken in spite of additional support with a plaster cast extending from the elbow to the foot.

FIG. 7(a).—Case No. 2. Devon bull calf aged 3 days. Transverse fracture lower third radius and ulna with over-riding.

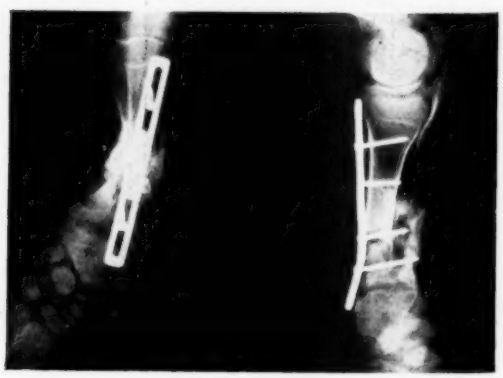

FIG. 7(c).—Note marked medial displacement of the lower fragment and bone rarefaction around the distal screws due to inadequate immobilisation.

FIG. 8(a).—Case No. 5. Shorthorn heifer calf aged 3 days. Oblique fracture lower third radius and ulna with upper fragment over-riding 1½ to 2 inches.

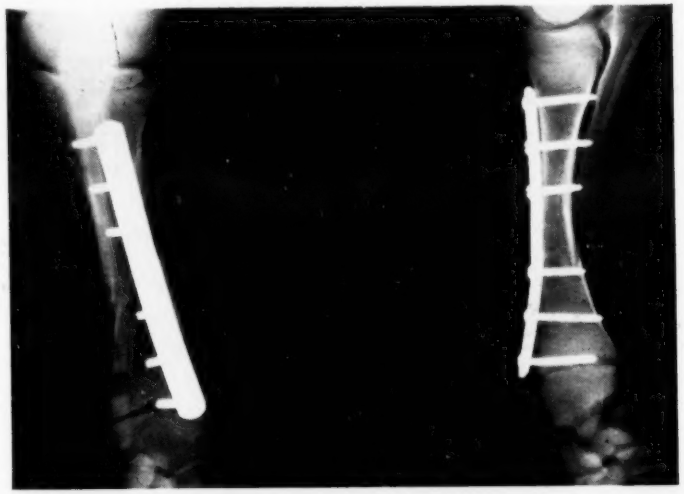

FIG. 8(b).—Immediately post operation. Satisfactory reduction and alignment. Plate moulded to the contour of the bone. Screws, with one exception, penetrating both cortices.

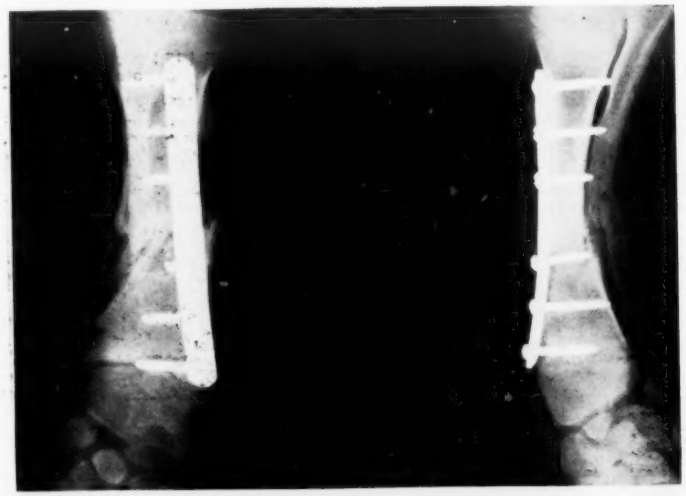

FIG. 8(c).—3 weeks post operation. Callus present and slight medial displacement of the lower fragment.

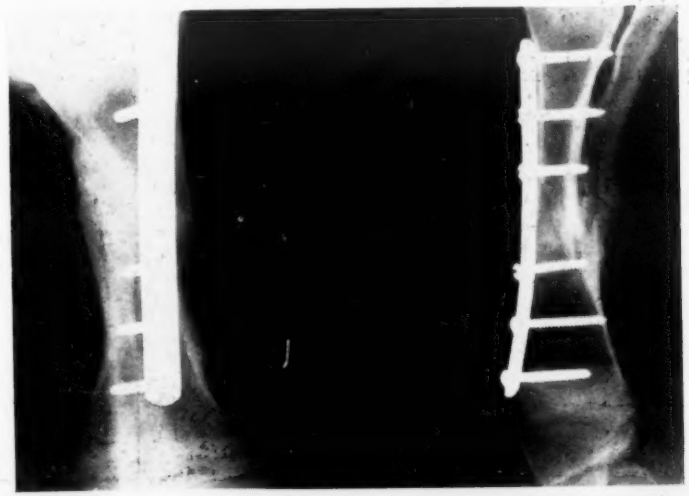

FIG. 8(d).—7 weeks post operation. Callus formation satisfactory. Note position of distal screw in relation to epiphyseal plate and compare with (b).

FIG. 9(a).—Case No. 6. Friesian heifer aged 3 days. Oblique fracture lower third tibia with over-riding 2 to 3 inches.

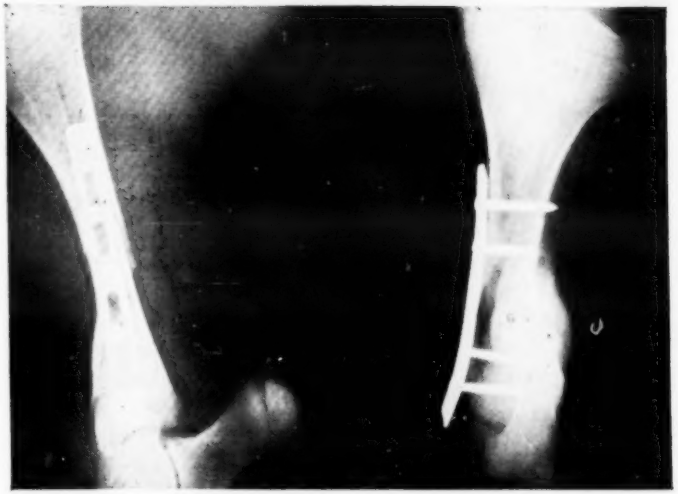

FIG. 9(b).—Immediately post operation. Satisfactory reduction and alignment. Eggers type plate used to allow choice of position when placing screws.

FIG. 9(c).—8 weeks post operation following the removal of the plate and screws. Satisfactory alignment maintained and good callus formation.

FIG. 9(d).—4½ months post operation. Contour of bone practically normal and early evidence of commencing canalisation of the medullary cavity.

in for more than 6 to 8 weeks because they will be buried in callus and difficult to remove. Intramedullary pins present a slightly different problem. By the time healing is established they are firmly embedded and therefore difficult to remove. Eventually they will be surrounded by a fibrous sheath and in many cases, at this stage, they become loose, ride up the medullary cavity and can be seen lying immediately subcutaneously. In this position removal presents no difficulties. It is not the author's practice to remove intramedullary pins until they have become sequestrated and are quite loose.

practically normal and early evidence of commencing canalisation of the medullary cavity.

Discussion

Before recommending the treatment of fractures in farm animals by open reduction and fixation, careful consideration must be given to the economic aspects. These measures should neither be advised nor practised unless they have very definite advantages over the time-honoured conservative methods. However, in many cases, to obtain the most satisfactory healing or to save the animal's life these more radical methods must be adopted. When dealing with farm animals no method is satisfactory, unless the animals regain a degree of locomotor efficiency which permits them to return to the herd or flock as economic units.

If the potential value of the animal warrants treatment then one has to decide whether or not the fracture in question can be satisfactorily treated. This requires the fractured bones to be fitted together and held firmly in position until healing is established. Perhaps the most important consideration is the age of the animal. The younger the animal the more hopeful the prognosis, for fractures heal more rapidly. More effective immobilisation at the fracture site can be obtained because the strains and stresses imposed during the healing period are less than in the adult. Attention has to be given to whether or not the fracture is compound, to the particular bone fractured, and the position and type of fracture. Transverse fractures of the shaft of the long bones can generally be immobilised either with a plate and screws or with an intramedullary pin. Comminuted fractures and those towards the extremity of the bone are often impossible to immobilise by mechanical means, and except in very young and small farm animals are hopeless propositions.

Post-operative control of the animal is a very real and difficult problem. In young cattle, pigs and sheep, this presents no great difficulty, as generally speaking sufficient immobilisation can be obtained to withstand the forces imposed by weight bearing. In the bovine animal over one year of age additional external support should be employed whenever possible using a plaster cast reinforced with a bar of iron. In spite of combining internal and external fixation the results are often disappointing. The older and larger the animal the poorer the prognosis.

Post-operative complications may result from either bad surgery or be unavoidable. These radical orthopaedic procedures should not be attempted unless the highest standards of asepsis can be practised, and even so, full use must be made of the antibiotics and sulpha drugs if infection is to be controlled. Careful attention must be paid to the selection of internal fixation appliances. Not only must they be the strongest possible consistent with the task in hand, but also they must all be of identical composition. Post-operative weight-bearing is unavoidable in animals. Within reasonable limits it is beneficial as use of the limb prevents excessive muscle atrophy and assists healing, but on occasions excessive force results in a complete disruption at the fracture site which is beyond further repair.

From the experience gained to date in the treatment of fractures in farm animals it is evident that radical orthopaedic procedures can serve a very useful purpose in selected cases. (See Figs. 8 and 9.) Many more cases will have to be studied, and the results carefully assessed, before one can be certain of the most satisfactory procedures to adopt and be able to give a definite prognosis for the various fractures encountered. Economics naturally have to be seriously considered, but all young stock, breeding and pedigree animals with fractures, are certainly worthy of careful consideration for the application of internal fixation methods before slaughter is recommended.

The general public are daily demanding more specialised services for their stock, and although the practice and principles of open reduction and fixation of fractures in farm animals have only recently been applied it is felt that these measures, with more experience, will become established procedures to the benefit of the farm animals and the agriculture industry. Present indications, however, suggest that surgery is a little ambitious for the conditions obtaining in ordinary field practice and should not be undertaken lightly on the farm.

Summary

1. The problems associated with the reduction, alignment and immobilisation of fractures in farm animals have been discussed and methods of overcoming them suggested.

2. The technique of exposing the fracture sites of the long bones and the methods employed for internal fixation have been described.

3. The necessity for radiological facilities and the use of the antibiotics and sulpha drugs have been pointed out.

4. The necessity for care in the selection, employment and handling of metallic implants has been shown.

5. Details of the treatment of fractures in 17 cattle, 3 sheep and 5 pigs are summarised.

Acknowledgments.—I wish to thank all members of the staff of the surgical team of the Department of Veterinary Clinical Studies for their help and assistance, Mr. R. G. Walker for his assistance at the operations and most helpful constructive criticisms, and Dr. L. W. Hall for ensuring a smooth anaesthetic recovery.

THE SPEAKER'S INTRODUCTION

Co'onel J. Hickman said that during the last four or five years he had taken a special interest in the treatment of fractures in farm animals. He was prompted to do so for two reasons. First he considered that in many cases the loss of valuable pedigree stock because of fractures was

most unsatisfactory, and not in the best interests of the veterinary profession. Secondly, due to their size and weight, special difficulties arose in the treatment of farm animal fractures, and therefore they presented an interesting surgical challenge. He had attempted in the paper to present those difficulties as he had found them, and the various methods employed in trying to overcome them.

It would be appreciated that the subject of the treatment of fractures in farm animals covered a vast and diverse field, and it had not been possible to treat the subject in anything other than a general manner. Each case had to be evaluated and treated on its individual merits. There were few hard and fast rules. The general principles of fracture treatment had to be applied to each individual case to the best of one's ability and with the facilities at one's disposal.

(By means of a series of slides, Colonel Hickman then proceeded to demonstrate some of the cases with which he had dealt.)

The Opener

Mr. A. C. Shuttleworth, in opening the discussion, said that when he was first invited to do so he was reluctant to accept the invitation, for although he had done much fracture work in the smaller animals, his experience in farm animals was limited. It occurred to him, however, that few people could have much knowledge of that specialisation as the opportunities were quite restricted. He decided that if he confined his observations to general rather than particular points, he should be able to add something to the discussion.

The author must be congratulated upon his venture into the field of fractures. It was a subject upon which little had been done—at all events in the larger farm animals. The paucity of numbers allowed no sound conclusions to be drawn, but it was a commencement. The lack of cases over a period of four years' work demonstrated the difficulty of choosing suitable patients for treatment. The factor which restricted the ventures was economic, and in Liverpool it was common to condemn fracture cases in farm animals unless they showed great promise of a return to near normal. He felt sure that the author had refused to undertake quite a number of cases which were unsuitable for one reason or another while building up the series. As he had remarked, careful choice was imperative if disappointment was to be avoided.

There was no claim for any revolutionary form of treatment in the paper. Indeed, it was apparent that much of the pioneer work done in the dog and cat had been applied to the larger animals. It had been shown that the principles of animal fracture treatment, the radiography and the internal and external forms of fracture immobilisation had been successfully adapted to the requirements of the new patients. It appeared that increasing familiarity with limb fractures of sheep, goats and pigs could make their repair as commonplace as in the dog and cat if economics permitted. He mentioned those species in particular because the sheep and goat were sufficiently light and agile to be able to manage an injured leg, while the pig, being a sedentary animal, could also cope with such damage. Treatment of fractures was most rewarding in the dog and cat. It was only slightly more difficult in the small farm-animals when transport was easy to suitable operating premises. It was, however, far more difficult in adult cattle, while in horses the difficulty increased greatly.

The first and most important requirement in a patient for fracture treatment was low body weight and the ability to manage an injured limb without tiring. Such animals were sheep, goats, young pigs, calves and possibly foals. The last required particular consideration. If only a few days old it would appear to be a good subject for fracture treatment. However, even if the patient accepted the restraint and survived the exhaustion of the treatment, it would quite possibly end in failure due to some slight fault in coaptation or alignment so that a crooked or twisted leg resulted, acceptable in slow-moving animals but not in the horse. In the horse, limb perfection was paramount and fracture treatment could rarely be meticulously accurate.

Sheep and goats were reasonably light in weight, very agile, and with a good sense of balance so that they managed on three legs very well. Their spare anatomy lent itself very well to surgery. Cases of fracture of the femur in those species at Liverpool were more simple than in the dog, for intramedullary pinning and bone healing were good.

Colonel Hickman had done remarkably good work in his pig subjects. In Liverpool good results had been obtained with plaster splinting of fractured tibia, but the author had plated the femur on several occasions with great success. The short and heavily muscled leg of the full-grown pig would not appear to be a good site for that interference. It was obvious that a plating of the femur could not be reinforced by an external plaster splint, and one would have thought that a plate would not stand up to the shearing effect of such a heavy limb swinging below it. However, it was apparent that that was not so. It was probable that the pig, being content to lie for long periods, took great care of the painful leg.

In cattle the limits of practicability in fracture treatment were being approached. The young of that species were reasonably light in weight, but were more clumsy than sheep and require time to develop the balance for going down and rising, and for standing on three legs while managing a painful fourth member. The older and heavier cattle became almost impossible. Their weight and clumsiness led to exhaustion and damage to the splintered limb. As with the horse, which was a surprisingly clumsy animal, no fracture control so far devised would stand up to such misuse.

Thus there was a barrier to much further advance in the treatment of the large animals. The barrier consisted in great body weight, lack of agility and balance, and such postural habits that the nursing of an injured limb for a long period was impossible. To pass that barrier a great improvement in the present methods, or a quite revolutionary technique would be necessary. For a satisfactory outcome, even of a simple mid-shaft fracture quite apart from the complications of those close to joint, meticulous methods must be used. The anaesthesia must be deep, prolonged and safe. Very powerful traction equipment must be devised to overcome the severe overriding that was often present. To forestall that the operation could not be long delayed or the muscle spasm became confirmed and the difficulties multiplied. Even in the case of a terrier-sized dog with a fractured long bone, if it were delayed for a week, owing to muscular contraction it became almost impossible to deal with it without severe handling of the limb. The author had mentioned the possibility of overcoming that by passing pins through each fragment, attaching a block and tackle, and then putting on traction. Mr. Shuttleworth had done that in the case of a dog with a fracture a week old, and it was impossible with ordinary traction to reduce. Everything stretched—the muscle, the leg, and even the block and tackle chain seemed to stretch, but not sufficient relief was gained at the fracture site. In trying to overcome overriding during the process of the internal manipulations little benefit was gained, and there was a danger of breaking down still further the fracture of the bone where leverage was being applied. The reduction, coaptation and correct alignment having been attained, special devices would be necessary to hold that position while the final splints were applied. Such heavy limbs were tiring to hold for long periods so that assistants could not be relied upon to support the correction without the risk of some slight displacement which would ruin the operation.

The final immobilisation must not rely upon bone plates, particularly those designed for human use. They were made for lighter bones and lighter limbs—for patients who lay in bed and were glad to do so, while the plated limb was frequently reinforced with plaster and splints. The intention of the bone plate was to immobilise the fracture site but not the whole limb. It was asking too much of that instrument to control the pendulum-like swing of the leg of a heavy animal.

The author had mentioned an unfortunate occurrence with an intramedullary pin in a cow, in which there was a gradual extrusion of the point of the pin into the stifle joint. That was a pity. It would appear that removal of the sharp point of the pin would be necessary. The intramedullary pin of suitable calibre should be strong enough for that work, but a more-detailed knowledge of the bone, joint and local anatomy was required. The pins used in the dog and cat did some damage very close to the

joints but recovery to full use was usual. Whether that damage to the joint neighbourhood would leave a permanent lameness in the large animals remained to be seen. The author's humerus repair by that method in a heifer was followed by a long lameness and might have been due to adhesions in the shoulder region.

A device on the principle of the Stader or Kirschner-Ehmer splint might be successful, but the equipment would have to be very powerful. The control of the fragments could not be by plain bone pins such as were used in the small animals. Experience at Liverpool had shown that they were very soon displaced by the rough usage they received in large animals. Stout, long and wide-threaded screws might be driven into each fragment as internal controls. They must be introduced by an electric drill. The external junction must be a powerful bar as the patient would place weight upon it. The fixing of the internal to the external part of the splint must be equally powerful, either by bolts or even welding if that were possible. Orthopaedics had been described as carpentry of bones, but in the large animals it was a heavy engineering job and must be approached as such. The limb must be able to take weight, the weight by-passing the fracture site through the splint. It was to be doubted whether such a service could be given on an appreciable scale in the foreseeable future. The occasional success would be a curiosity. The economic factor was paramount, while the humanitarian question was also one which must be considered.

On the techniques, materials and methods used by the author he had little comment to make. It was obvious that orthopaedic equipment, plates, screws and instruments required special designs for veterinary work. Those provided by instrument makers and to the requirements of the human patient were often wanting. Finer screws and plates were necessary at times for the dog and cat, while more massive instruments were called for in the large animals. Such a wide variation in sizes to supply such a small market was a problem that was not likely to be easily solved.

The General Discussion

Mr. M. A. Crawshaw (Newbury) said: Dr. Böhler of Vienna, in his book dealing with the treatment of fractures in man, advocates the use of local anaesthetic injected into the blood clot at the site of the fracture to reduce the spasm of the muscles. With aseptic technique and the use of antibiotics there is little danger from the use of such a method. Colonel Hickman has stressed the difficulty of overcoming the muscular contractions in cases of fractures in farm animals. Has he considered the use of local anaesthetic in this connexion?

Mr. C. T. Murphy (Colchester). The late Professor Imrie of the Glasgow Veterinary College, published an interesting case in the "Veterinary Journal" in the early 1920s. He was called to a Clydesdale mare which was heavy in foal and he found she had a fracture of the fore leg. He placed the mare in slings and bandaged the leg in the hope of keeping the mare until she foaled. A strong sheet of canvas supported by wooden splints was strapped over the bandaged leg to prevent movement and a hole was dug in the floor into which the animal's foot was placed, thus taking the weight off the leg. A chain was attached to the shoe and led underground to pass through an arrangement of pulleys on the wall of the stable. Weights were attached to the hanging end of the chain and in this manner traction was produced. The mare remained comfortably in the slings and foaled on time and the fracture made such a satisfactory recovery that, after suckling the foal, she was put to work. Only very slight displacement was seen when the leg was viewed from a certain angle.

"I agree with one speaker who has already said that purchasers of racehorses buy them on the history of their performance and not on their appearance. It is quite impossible to assess the value of a racehorse from his appearance no matter how beautiful he is. One often sees the plain, unattractive-looking horse sound and outstanding in the performance of his work, whereas many beautiful horses are unsound and useless. I would like Mr. Dawes to differentiate between good conformation and beauty."

Mr. James Roberts (Newmarket). I wish to add my congratulations to the author and I am happy in the realisation that so much had been done in tackling a problem left unapproached for so long. I agree with Mr. Shuttleworth that specially designed apparatus would have to be made, and my experience has verified the observation of the author that screw heads tend to be sheared off by bone plates. I have attempted to overlook such problems by using heavy screws up to ¼ in. in diameter with coarse threads. These screws were not the answer, however, as I have known them pull out of cortical bone in a case of oblique fracture of a humerus in a three-month-old thoroughbred foal. Careful examination showed that in spite of a very firm initial bite at the time of insertion the screw thread had not cut sufficiently deeply into the sides of the bony canal. I would suggest, therefore, that a modified technique is necessary when inserting orthopaedic screws into the dense cortical bone of farm animals and would be glad to have the author's comment. I would suggest, after drilling the channel through both cortias of the bone, that a screw thread be tapped into the bone channel and that a matching threaded screw be used. This screw should match and seat as precisely as does an engineer's screw into its block.

I have noticed that fractures of limb bones which were initially simple when examined on the stud or farm had become comminuted and sometimes compound by the time they arrived at the hospital. I suggest, therefore, that it might be a policy to take the surgical equipment to the stud or farm, and operate there rather than to run the risk involved in transport.

As fracture cases are comparatively rare some discussion should take place whenever possible between veterinarians before surgery is commenced. Otherwise, techniques which had already proved ineffective may be repeated unwittingly and valuable material be wasted. If the new technique suggested after due consultation proves a failure, further information would at least be added to the general fund of knowledge and thus would be available for the next emergency.

The Replies

Colonel Hickman, in reply, said that he agreed with most of the speakers that the weight of the animal was the biggest problem associated with the treatment of fractures in farm animals. The success he had had in treating pigs was probably due to the fact that they looked after themselves. They remained quiet, made no attempt to get up, and after about 3 weeks it was necessary to help the animal to its feet and encourage it to start moving around.

He was rather surprised that Mr. Shuttleworth had been unable to reduce some canine fractures. It was true that some neglected fractures were very difficult to reduce, but he had found that by adequately freeing and trimming the bone ends such difficulties could be overcome.

He did not consider that external splinting with pins and clamps could give adequate immobilisation at the fracture site when dealing with the larger animals, but occasions might arise when this method could be employed satisfactorily in conjunction with others. Internal fixation with an intramedullary pin gave stronger support at the fracture site than a plate and screws, but was not suitable in all situations. From the commencement of this work it was soon realised that the standard plates and screws were not strong enough and so extra long and thick plates and screws were being specially made.

The use of local anaesthetics at the fracture site to produce muscle relaxation had not been tried but in his experience the most satisfactory method was to produce muscle fatigue by prolonged and continuous traction.

He was not familiar with the case quoted by Mr. Murphy, but in the literature one would find numerous cases of fractures in horses which had been treated successfully by the conservative methods, but in the majority of these cases there was no overriding of the fragments.

The diagnosis of fractures of the pelvis and femur in recumbent cows was difficult. Manipulation of the limb by an assistant whilst rectal and other examinations were conducted could be of assistance. He preferred coarse- to fine-threaded screws as they were less likely to pull out, but the most important point was to ensure that they penetrated both cortices.

Following open reduction and fixation operations the quietness of the recovery period was most important. To a great extent this depended on the temperament of the

animal. Undue struggling and excessive weight-bearing could easily bring about a complete disruption at the fracture site.

Mr. Shuttleworth also in reply, said that in the case of the fractured femur in the cow, all he could say was that if the lower part of the limb were lifted in the normal animal, the patella would slip off, and one could straighten the hock so that it was possible to feel the patella slip back. In the case of a fracture, that could not happen; the patella stayed in position, and that method might be adopted in the case of the cow.

The Chairman, Professor Messervy, said that in dealing with fractures in small animals it was necessary to retain a knowledge of physiology.

On the question of relaxing, it had been pointed out that adequate anaesthesia was essential. He had endeavoured to repair fractures in animals, and the results had not been entirely successful. He had tried relaxants, and his experience of them used experimentally in the ruminant was disastrous. The animal remained in a state of shock and did not recover.

Veterinary and Human Medicine

BY

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Introduction

SAMUEL JOHNSON defined a veterinarian as one skilled in the diseases of cattle, and quoted Sir Thomas Brown's remark of 1646 " that a horse has no gall, is not only swallowed by common farriers, but also received by good veterinarians, and some who have laudably discoursed upon horses."

The distinction thus drawn, over 300 years ago, between the common farrier and the good veterinarian, is reminiscent of the difference between the barber surgeon and the physician, and the history of the veterinary and medical professions bears many striking similarities. They have both, at worst, been described as quacks and " leeches " and, indeed, there were times when the Anglo-Saxon " leech books " and the " cow and beast leeches " were the principal means of keeping the knowledge alive.

Our ancient history has many parallels. Were we not both mentioned by King Hammurabi of Babylon more than 4,000 years ago? Veterinarians were then the " doctors of oxen and asses " and, indeed, as the derivation of the word veterinary implies, the care of beasts of burden was of the first importance in societies in which they were the only means of transportation over land. It is probably not too far-fetched to suggest that the practical knowledge of animal diseases in ancient times exceeded that of the physicians, for human medicine was inextricably bound up with the supernatural.

In medieval times, also, the " Master Marshals " of London, whose trade guild was granted an ordinance in 1356 by the Mayor and Aldermen, must have been men of substance, both in civil and military affairs, but, like medicine, the veterinary art later fell into disrepute.

Towards the end of the eighteenth century the climate of public opinion changed, and it is interesting to speculate on why it did so. In human medicine the reasons for the developments of the 18th century are fairly clear. The work of Sir William Petty, John Graunt, and others, at the turn of the century, had demonstrated the cost of epidemic disease, such as the Plague of London, and the waste of human life. The realisation had also grown that it was foolish to let skilled work-people die if their lives could be saved. A kind of hard-headed business philanthropy inspired the founding of hospitals and dispensaries in the first half of the 18th century, and public opinion became increasingly favourable, as the century advanced, towards the practical application of scientific knowledge. Lind's Treatise on the Scurvy, and Pringle's advocacy of better ventilation of prisons and gaols, are only two examples of this.

I imagine that a similar process lay behind the resurgence of " the practical application of sure and scientific principles to the preservation of health in animals," to quote the *Gentleman's Magazine* for 1790, but here the stimulus may have been the great losses from recurring epidemics of cattle plague, or rinderpest. The fact remains that in 1791 the efforts of the Odiham Agricultural Society, aided by a number of noblemen and gentlemen interested in the welfare of horses and cattle, led to the establishment of a veterinary college in London, and Charles Vial de St. Bel, from the Lyons Veterinary School in France, was established as the first professor. In 1823, William Dick, helped by the Highland and Agricultural Society of Scotland, founded the Edinburgh School. The subsequent rivalry between the leaders of those schools belongs to your private history, but it is interesting to note that the impetus for the foundation of these veterinary schools came from those with agricultural interests and, presumably, a strong economic motive. With the exception of John Hunter the links with human medicine appear to have been slender, although the *Medical Journal* for 1804 has a friendly reference to the bringing of the therapeutics of the human body to veterinary science.

Then, in 1796, came a discovery which was to prove the starting point of many of the preventive measures available to-day. William Jenner's demonstration that cowpox protects against smallpox was, indeed, revolutionary. The distinction between human and animal was no longer tenable so far as medicine was concerned.

The subsequent development of the two professions proceeded on similar lines. The Royal Charter of 1844 brought into being the " body corporate " of the Royal College of Veterinary Surgeons; the Act of 1881 distinguished qualified from unqualified men and introduced the term " qualified veterinary surgeon," and in 1949 practice by an unqualified person was finally made illegal, except for certain minor treatments and operations. The scope of teaching has extended from apprenticeship and two sessions in 1844, to a four-year course in 1895, and a five- or six-year course to-day. There are now approximately 6,000 names on the Veterinary Register.

Scientific Developments in Veterinary and Human Medicine

Modern veterinary medicine owes its pattern of organisation to the help it received from agricultural interests, and it is powerfully influenced in its work by economic considerations. Compassion for suffering in animals is as important, and as manifest, as it is with doctors, but veterinarians have, in effect, a double responsibility, for it is their duty also to prevent and treat disease in animals for the benefit of mankind. The approach is, therefore, more severely practical. Is it economically sound to treat this, or that, disease in a herd, or flock, or individual animal? If not, then the alternative is to settle the matter by terminating life. This means that the vet-

erinary surgeon is not only saved a number of vexing ethical questions, such as those relating to euthanasia, therapeutic abortion, and artificial insemination, but he is also unlikely to be overwhelmed by a public demand for the latest remedies regardless of price or efficacy. This difference in approach has had another, and more important, result. The prevention of disease is a major consideration in veterinary science. and has been so for a longer time than in human medicine. As Professor Pugh pointed out, in his Inaugural Lecture to the University of Cambridge, it is unlikely that curative medicine in animals will ever require to develop the same skill as in human medicine. The necessity is not there, the emphasis is on the maintenance rather than the restoration of health and will be even more so in the future (Pugh, 1955).

A hundred years ago human and veterinary medicine were still in the stage of empiricism, with reliance being placed almost entirely on clinical diagnosis and treatment with traditional remedies. In Britain the " era of sanitation " had just begun, and the physical environment, especially in the large centres of population, was coming under attack. The ancient methods of sewage disposal, the faulty water supplies, bad housing and unhealthy working conditions, and pollution of the atmosphere, were recognised as powerful influences in the cause of disease in the mass, but prevention of disease in the individual or improvement in his personal health, and the control of infection, were as yet unthought of.

Then came the pioneers of bacteriology, and at once veterinary medicine leapt ahead. To-day it is recognised that both methods of prevention are required, by control of the environment and the immunisation of the individual, but this was not always so.

Louis Pasteur was made an Honorary Associate of the Royal College of Veterinary Surgeons in 1881. It was in 1857 that he produced his paper on lactic fermentation, and it was not long before he turned his attention to the diseases of animals. By 1866 he had investigated the silk-worm disease, pébrine, and demonstrated its contagious nature, and soon afterwards he put to practical test his reflections on the lessons to be learned from Jenner's smallpox vaccination.

The story of Pasteur's successes with immunisation using attenuated forms of organisms is well-known. First fowl cholera, then anthrax with a mortality of 10 per cent. successfully reduced to less than one per cent. in some areas, next swine erysipelas with attenuation of virulence of the causal organism by passage through rabbits, and so to rabies. By 1885 he had mastered all these diseases, and immunised his first human patient. In 1888 the first Pasteur Institute was opened, but he was by now a sick man, and I am glad that you honoured him so much earlier.

Those were indeed stirring times. As Professor Miles has pointed out, the Germans, led by Koch, had concentrated essentially on techniques, and the French on the possibilities of immunisation (Miles, 1955). In Britain we continued to develop our attack on the physical environment, and it was the surgeon, Lister, who first realised the full possibilities of the new discoveries in bacteriology. The impact on veterinary surgery was, however, less marked than in the human field (Edwards, 1951). So rapid and exciting were the advances in bacteriology that expectation outran performance, as we have seen happen more recently with the antibiotics. Even to-day the lesson has yet to be learned that there are no permanent " short cuts " in medicine.

By 1886 Salmon, whose name is now ominously associated with the growing importance of the Salmonella infections, and Theobald Smith, were already investigating hog cholera, and 3 years later, in 1889, von Behring and Kitasato extended the new discoveries to tetanus and diphtheria. By 1892 Ivanowski had discovered the first known virus, causing mosaic disease of tobacco plants, and before the century ended Loeffler and Frosch had shown that foot-and-mouth disease was also due to a filterable agent. It is noteworthy that most of these discoveries, in addition to Koch's work on the tubercle bacillus, were made in the field of veterinary medicine.

The Triumphs of Veterinary Medicine

An observer like myself is, perhaps, better able to note and record the subsequent triumphs than those whose work lies in the daily application of the results of those discoveries. I will make no apology, therefore, for examining the record of achievements.

As early as 1705 Thomas Bates had advised King George I that cattle plague could be eradicated, and at the beginning of the 19th century Edward Coleman had succeeded in reducing to negligible proportions the losses from pneumonia and other respiratory disease among army horses by insisting on adequate ventilation of the stables, as had Pringle with barracks some fifty years earlier.

In 1879 Thomas Walley listed the 4 bovine scourges in Britain as being cattle plague (rinderpest), contagious bovine pleuro-pneumonia, foot-and-mouth disease, and tuberculosis (Edwards, 1951). To-day it is the proud boast of veterinarians that cattle plague and pleuro-pneumonia have been eradicated from the British Isles, together with a number of other conditions, and that foot-and-mouth disease and tuberculosis are under control. In 1955 there were only 9 outbreaks of foot-and-mouth disease in Britain, and 6 of these were traced to imported meat and meat wrappers (Ministry of Agriculture, 1955).

Tuberculosis demands special mention. In 1931 some 40 per cent. of the cows in this country were infected. The first Tuberculosis (Attested Herds) Scheme was introduced in 1935. In 1938 a tuberculin survey showed an overall incidence of 13 per cent. of reactors, with the greatest weight of infection around the large cities and industrial centres. Meanwhile a State Veterinary Service had been set up under the Agriculture Act of 1937. At the end of 1939 some 6 per cent. of cattle were in attested herds; by 1943 the proportion had risen to 19 per cent.; at the end of 1955 it was 62 per cent. and accelerating rapidly. That means that over 6 million cattle are now in attested areas and attested herds as compared with less than 6,000 in 1935.

To-day more than two-thirds of all cattle in this country are of attested status, and at least 75 per cent. of the milk sold in Great Britain is produced from tuberculin tested herds as compared with 15 per cent. 10 years ago. It can be claimed, and with justification, that the end of the campaign is in sight and will be reached in about 5 years' time. Already I have to listen to the half-serious comments of the members of this veterinary school to the effect that cattle must be protected against the human case.

The most highly infected areas are usually near large cities and industrial centres, where the cattle population is dense and milk production intensive, with close housing of cattle. The next step is the formation of Area Eradication Plans, with Attested Areas in which all herds have been tested twice, reactors removed, and disinfection completed. One-fifth of the total cattle population, that is two million cattle, is now in Attested Areas with a further four million in attested herds.

The Organisation of Medicine

At the beginning of this century the advances in human medicine had been mainly in the fields of surgery and anaesthesia. The physicians had few specific remedies or aids to diagnosis and it was the golden age of " the doctor " of popular imagination, the silent bearded figure sitting through the night at the bedside of a feverish child, in a room filled with massive Victorian furniture. In the human preventive field the main preoccupation was still with environmental sanitation, but there was an increasing awareness that the great epidemic diseases might be capable of reduction in virulence, although control seemed as yet out of the question.

In the veterinary field the position was rather different. There was already the knowledge that certain plagues could be stamped out, if determined efforts were made, by means of quarantine and slaughter, and other diseases controlled by immunisation, but it is doubtful if the members of the two professions were, in fact, conscious that they were working in similar fields, in spite of the advances in biology, physiology, and pathology.

Then came the dramatic effects of three wars. The Boer War led to the Interdepartmental Committee on Physical Deterioration, and the awakening of the interest of the State in personal human health, with schemes for the control of tuberculosis, a school medical service, the encouragement of maternity and child welfare services, and the first National Health Insurance Scheme.

The First World War saw the introduction of medical examinations and " inoculations " on a massive scale, with great advances in surgery, further attempts to control the venereal diseases and tuberculosis, and to improve the health of mothers and children, and a national interest in nutrition because of rationing. In 1919 the Ministry of Health was established, with a Minister responsible to Parliament for health matters.

Twenty years later the Second World War broke out, and we have emerged from that with a comprehensive National Health Service as part of a system of social legislation. The primary interest in human medicine is still in the clinical care of the sick person, but emphasis is increasingly being laid upon prevention and research.

The orientation of veterinary medicine has always been towards prevention. The costly curative processes of human medicine are required only for exceptionally valuable animals, or for reasons of sentiment, and the health of the herd and flock has always been the first concern of the veterinarians. Indeed, the veterinary profession has the best of both worlds, for the private practitioners are also employed part-time by the State.

The universities have become increasingly aware of the importance of veterinary medicine, as is shown by the formation of new Veterinary Schools at Bristol and Cambridge in 1949, and the extension of those already in existence, while the volume and character of research now being undertaken is such that in the laboratories there is only one medicine, for the problems under investigation are common to man and animal.

Some Current Problems

Taking the world as a whole a major problem is now one of increasing numbers of the human population. With the control of the major killing diseases, especially those occurring in infancy, the numbers of people are increasing rapidly, especially in those countries hitherto regarded as under-developed or backward. " Civilisation " has meant, for human beings, industrialisation, and the growth of towns and cities, with migration from the country. To meet the increased demands for food there has developed the intensive domestication of animals, often under equally unnatural conditions. In the words of Edwards, " The selective breeding pursued for a century or longer has transfigured the constitution not only of individuals but of whole lines or races of stock, so as to render them, if not hereditarily less competent to survive and to reproduce their kind, at least more prone to the impact of adverse influences in the environment, and thus to discharge those excess functions that had been induced in them. Even their normal functions, concerned intimately with survival and reproduction, eventually were becoming curtailed. As with ' civilisation ' so also with ' domestication.' " (Edwards, 1951).

If that picture is true, and I see no reason to doubt it, then it is impossible to exaggerate the importance of the work of the cattle-breeding centres, and similar research stations. It seems to me quite remarkable that the Reading Cattle Breeding Station, for example, should be able to report a conception rate of 62.4 per cent. in 41,000 cows artificially inseminated, using deep-frozen semen as a routine (Ministry of Agriculture, 1955). The fact that bulls' semen can be fertile after 12 months' retention at $-70°$ C. is, to me, a discovery of greater importance even than that of the antibiotics, for it means that the supply of cattle of good stock can be maintained all over the world. It is worth noting the Reading figures in detail. In 1955 artificial insemination resulted in 9,004 live heifer calves (368 dead) and 9,748 live bull calves (307 dead), with 308 abortions.

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At Ruthin Castle the overall conception rate for 34,717 animals was 65 per cent.

The current work on infertility will also add to human knowledge, and it is not impossible that the veterinary researches into the venereal transmission of various organisms by infected males may throw light on certain obscure human disease conditions.

A current problem of almost world-wide importance is the increasing incidence of infection with the Salmonella group of organisms. I need not remind you of the disastrous effects of pullorum disease, with gross ovarian degeneration in the majority of naturally infected fowls, nor of the infection of turkeys with *S. typhi-murium*, but you may be as interested as I was to learn of the presence of *S. gallinarum* in the sparrow (Ministry of Agriculture, 1955).

The year 1955 saw a considerable increase in clinical cases of Salmonellosis in cattle, especially south of a line from Aberystwith to the Wash, and on one farm *S. typhi-murium* was isolated from the cats. The high incidence in rats and mice is already sufficiently well known. There were also 489 confirmed outbreaks of fowl typhoid (*S. gallinarum* infection) in that year, with the highest incidence in Yorkshire, the Midlands, and mid-Wales. Incidentally, these outbreaks demonstrate clearly the superiority of veterinary methods of control over the human, for it is only necessary to administer furazolidine for 10 days and then to transfer the birds to fresh accommodation on clean ground. A rapid blood test is then done, the reactors destroyed, and the disease is eradicated.

There is clear evidence of a marked increase in human Salmonella infections in Great Britain over the last decade or so (Savage, 1956). The number of outbreaks of food-poisoning from this cause is increasing year by year.

Side by side with the extension of Salmonella infections in animals has gone a rise in symptomless cases, or carriers, in human beings, and Sir William Savage names 5 factors contributing to this. They are the changing food habits of the people, with lack of hygienic control of food places; the extension of bulk preparation of packaged and other foods under factory conditions with an inherent increase in risk; the extensive and extending use of bulked eggs in confectionery; the extension of reservoirs of Salmonella in animals, and the increase of human carriers. He points out that methods which are harmless in the domestic kitchen are fraught with risk in the communal kitchen. In 1955 there were approximately 9,000 incidents of food-poisoning in England and Wales, many of which were due to Salmonella infections. *S. typhi-murium* was responsible for 50 per cent. of all recorded incidents in 1954. This is truly a zoonosis requiring our united attention, for there are more than 300 different serotypes and all are potentially pathogenic (Buxton, 1957).

The Zoonoses

The ugly but expressive word, zoonosis, said to have been coined by Virchow (Heisch, 1956), and meaning an animal disease capable of being transmitted to man, has come to the fore, particularly since the Second World War. One of the functions which the World Health Organisation discharges particularly well is the definition of new fields of study, and the encouragement of investigation into the problems coming under that definition. One such recent activity has been in veterinary public health work, with particular reference to " those diseases which are naturally transmitted between animals and man " (W.H.O., 1956).

The W.H.O. Reports stress the large economic losses in trade and agriculture caused by these diseases, in addition to human ill-health and poverty, especially in rural areas, and the conclusion is reached that " It is certain that the prevention and elimination of zoonoses in man depends in large part on the control of these diseases in animals " (W.H.O., 1957).

The major zoonoses in Europe include bovine tuberculosis, brucellosis, rabies, and hydatidosis, and here also the British record is worthy of examination. Only 1,251 animals with *clinical* tuberculosis were slaughtered in 1955, with a one per cent. error found at *post mortem*, as compared with approximately 24,000 slaughtered in 1936. So accurate are the modern methods of detecting this disease in the early stages that of 12,000 *reactors* slaughtered in 1955, some 83 per cent. showed evidence of tuberculosis at *post-mortem* examination. The problem is not yet completely solved, for in 1955 the divisional veterinary officers received 718 notifications from medical officers of health that tubercle bacilli had been found in bulk samples of milk. As a killing disease, and as a cause of incalculable distress, bovine tuberculosis is, however, no longer a baffling problem, and the nation owes the veterinary profession a debt of gratitude which it is as well to record now, for memories are short.

Brucellosis is to me an elusive condition, but it seems clear that here, also, veterinarians have the measure of it in Britain by way of sanitary control and vaccination.

Rabies is certainly under control, for there has been no case in domestic animals in this country since 1922 except among those in quarantine (Ministry of Agriculture, 1955). Hydatidosis does not appear to be a major problem in this country.

Although the major zoonoses of Europe, as defined by the World Health Organisation experts, are under control in Britain, Meyer has pointed out that at least 80 infections or diseases of domestic and wild vertebrates are potential threats to man's health (Meyer, 1953), and so there is no cause for complacency.

One interesting result of recent researches has been the demonstration that these problems are truly world-wide. In the words of the World Health Organisation Report, " The emergence of new zoonoses, or the uncovering of unsuspected human-animal relationships in communicable diseases, are therefore to be expected, *e.g.*, bird reservoirs of arthropod-borne virus encephalitides, wide prevalence of bovine and other animal leptospirosis in many countries, bat-rabies in the Eastern Hemisphere, and widespread mammalian reservoirs of psittacosis " (W.H.O.,

1956). It is customary to regard tropical and sub-tropical countries as the nurseries of many of these diseases, but it is surprising to find how extensive they are in arctic areas. Trichinosis, for example, has been found in whales, seals, polar bears, and other wild animals in Alaska. In Greenland in 1947 sledge dogs, walruses, polar bears, arctic foxes, the bearded seal, and the white porpoise were all found to be infected, with dogs as the main reservoir. Hydatid disease occurs under arctic conditions in wild herbivorous animals, dogs, rodents, and man, and the leptospiroses are also a significant problem in Alaska (Meyer, 1953).

Nutrition

While it is attractive to dwell on the diseases which may spread from animals to man, and vice versa, this is by no means the whole story. Medicine, in the limited sense of the study of the causes, prevention, and cure of disease, can claim only a part of the credit for the advances in human and animal health and welfare which have occurred in the present century. A large share must go to the improvements in nutrition, and in the general standards of human living and animal management.

One result of the recent intensive studies of the world pattern of disease has been the realisation that deficiency of proteins of animal origin, and of vitamins and minerals, underlies much of the suffering in the world. At its most dramatic this deprivation appears under such names as Kwashiorkor, "sugar-baby," and the like, but its possibility touches, in fact, every individual in the world, for a successful arrival on this earth, and the ability to stay alive in the critical early weeks of life, depend to a very considerable extent on the state of nutrition of the mother. The proper growth of teeth, and the functioning of the blood-stream, are dependent on an adequate supply of proteins, vitamins, and minerals.

In passing, I was interested to read that the most critical period of life for the pig is identical with that of human beings, namely that immediately following birth, and that the causes of death appear to be very similar. It was also interesting to see that veterinarians have discarded the view that many of the deaths of newly-born pigs are due to over-laying, for it is now recognised that some are due to hypoglycaemic shock while others are probably due to a virus infection. There is evidence that sudden death in human infants is not commonly due to mechanical asphyxia, but to some overwhelming infection, also probably by a virus.

The principal sources of first-class protein, and also of much of the required minerals and vitamins, are meat, milk and milk products, fish, poultry and eggs, and it is here that the veterinary profession exercises a responsibility which carries it into the fields of food, agriculture, and economics. By reducing the loss from disease an increased supply of food for the world is ensured, and the value of a large and important industry improved, for the capital invested in cattle, poultry, and pigs, must be almost incalculable.

It is inevitable, therefore, that the disease conditions in animals which are of importance to human beings should receive first consideration. In cattle, for example, mastitis and impaired fertility have been responsible for enormous losses. Meyer has estimated that 25 per cent. of all cows in the United States are infected with organisms that cause mastitis, and that this infection reduces milk production in the infected quarters of the udder by about 22 per cent. (Meyer, 1951). It is now possible to treat mastitis simply and quickly, but the need for facilities for laboratory investigation, and the cost of the antibiotics, affect the cost of milk production. The ease with which antibiotics can be introduced by the farmer into the affected quarter of an udder makes one anxious about the development of resistant organisms.

The numbers of poultry in the world are so great that it would, at first sight, seem hardly worth while bothering with losses from disease, but here also there are important human and economic factors. American analyses estimate that every year 70 million laying hens of an annual crop of 425 million die. When the mortality rises over 25 per cent. the question of economic loss has to be considered. Other human interests are also deeply involved, for many of the food-poisoning outbreaks are traceable to eggs and egg-products, and it would appear that more attention could be paid to the conditions under which poultry, both live and dead, are kept and handled.

Similar considerations apply with even greater force to the loss of pigs before they reach marketable condition, for these animals share a number of bacterial and parasitic diseases with man. They also consume a great deal of costly food which is wasted, in addition to the meat and meat products, if the animal dies of disease.

The economic burden in the United States of America from animal diseases was recently put at $2,000,000,000 a year, and that is in a country which takes pride in having one of the most efficient veterinary services in the world (Meyer, 1953). If much of the loss from disease is capable of being prevented we need not worry unduly about the world food situation for a long time to come, for the control of the great animal plagues in tropical and sub-tropical countries should produce results as remarkable as those following the control of malaria in human beings. World livestock numbers are already at record levels and feed supplies ample. A record world output of over 24 million tons of fats and oils was available for use in 1955, and exports of meat from the major exporting countries were about 7 per cent. larger than the year before (F.A.O., 1956).

The Future

We live, in effect, in two worlds which are speedily becoming one again, from the medical point of view. Roughly one-sixth of the people of the world, having accumulated wealth and knowledge as a result of industrialisation, have so succeeded in improving their environment that they have conquered the great killing diseases of infancy and childhood, and they have added considerably to their expectation of life. The principal causes of death in these societies are now those of middle age, and

consist of the disasters affecting the heart and blood vessels, and cancer. Among the principal causes of illness, apart from death, are infections of the respiratory tract, "rheumatism," minor mental disorders, and accidents. The virus infections, and particularly those with an affinity for the nervous system, are on the increase.

About the rest of the world it is only possible to generalise, for accurate statistics are hard to come by, but, in general, the picture was, until quite recently, one of severe malnutrition combined with many infectious and parasitic diseases. Within the last 10 years, however, the scene has changed in remarkable fashion, for the great killing diseases are being brought under control, the numbers of people are rising rapidly, and the nutritional deficiencies are becoming more obvious.

In the problems confronting these two worlds the interests of veterinary and human medicine are becoming one and the same. Indeed, just as there is only one derivation of the word medicine, from the Latin "to heal," so there can only be one medicine in the future, for the purpose of both professions is to improve the health of mankind.

The provision of a reasonable standard of nutrition, both in quality and quantity, is the responsibility of the experts in food and agriculture, with advice from the veterinarians on how best to protect and improve the health of the herds and flocks. The basic principles on which that advice rests are common to all vertebrate animals including man. The essentials of prevention are the same and also those of treatment, both medical and surgical. Advances in one field must therefore be of benefit to all. It is for this reason that I and my colleagues in this university have welcomed so warmly the establishment of the Cambridge Veterinary School, for we believe that in the years to come the comparative study of human and animal disease will provide the answer to many of the problems now confronting us. Already we have seen some of the benefits in experimental surgery and in anaesthesia. In microbiology it is impossible now to distinguish the veterinary from the medically trained workers for both, as the Professor of Microbiology at Otago said in his inaugural lecture recently, "love the little beasts for their own sakes" (Miles, 1956).

I have felt for some time that the solution to a number of obscure neurological problems in human beings will come from research into animal diseases and, indeed, it would not surprise me if the solution of the greatest problem of all, the cause or causes of cancer, came first from a veterinary school. As Edwards, on whose writings I have drawn so freely in this paper, has said, "What the connexion can yet be between such growths in which there is a demonstrable virus and those in which none has been revealed but can be produced now almost at will by certain chemical agents, seems to be within sight of resolution. Blakemore's important work on the neurolymphomatosis of fowls, commonly known as fowl paralysis, in which, by careful breeding and observational technique, he was able to disclose an antecedent generalised virus infection, may not be insignificant in bridging the gulf between tumours of virus and non-virus origin" (Edwards, 1951).

There is one development in the veterinary field which I should like particularly to see, and that is the further encouragement of ecological studies, using that term as defined by Field-Marshal Smuts to mean the "holistic" approach to human problems. Medicine is now so highly specialised that there are certain advantages in having a few people whose business it is to try to see the broad outline of current trends.

One such example is the development of organisms resistant to the antibiotics. We are, if I am not mistaken, about to reap the whirlwind, in the form of resistant staphylococci in hospitals and elsewhere, and we may yet have to return to the strict Listerian concepts of antisepsis on this account. In the animal world even greater reliance is being placed on the antibiotics, including their use in normal feeding and in the preservation of food. It may be found that the natural intestinal flora of domestic animals have been so altered by this means that deaths will occur, especially in young animals, from hitherto harmless commensals such as the coliform organisms which have taken on a new character. That has already happened with strains of *Escherichia coli* (Williams Smith & Crabb, 1957). Professor Pugh, in addition to referring to Williams Smith and Crabb's work, has also pointed out that mastitis in cows, due to strains of staphylococci resistant to penicillin and the tetracycline compounds, appears to be on the increase (Pugh, 1957). He has also referred to the comments of Ella Barnes on the danger that antibiotics used to preserve food might eliminate the normal spoilage organisms. There could then be heavy contamination with resistant pathogens but no evidence of this from flavour or appearance (Barnes, 1956).

Somewhat similar considerations govern the use of the new insecticides. With the realisation that mosquitoes are becoming resistant has come the need to speed up anti-malarial campaigns, so that the maximum effect may be gained in the few years that remain, before resistant strains become too numerous.

There is another way in which a "broad" approach may be advisable, and that is in the study of the natural history of certain human and animal diseases which wax and wane in disconcerting fashion. Each generation tends to regard reappearances as a new phenomenon, and to take credit for new remedies when the disease dies down. At the risk of appearing to be obsessed with the problem of cancer, may I suggest that someone be charged with the responsibility of examining the records of the incidence of cancer in domestic animals seen in the various hospitals, clinics, and dispensaries, over the past 40 years. It would then be possible to compare any changes found with the altered incidence of the various sites of cancer in man.

Conclusion

I hope that I have said enough to make it clear that in the future the study of medicine must embrace both man and animals. At the moment the medical

profession is painfully preoccupied with finding its place in a welfare state, and it is divided administratively into hospital and specialist services, general practitioner services, and the local health authority preventive services. The veterinary profession has no such anxieties, for in his part-time veterinary service the general practitioner works in the closest association with the full-time officers of the Ministry of Agriculture, Fisheries and Food.

It seems to me that the focal points for both our professions in the future must be the university medical and veterinary schools, and I would like to conclude with a plea for joint facilities for post-graduate study and research. Only by this means can we ensure that progress is co-ordinated and that the results, good and bad, of all the new discoveries and advances are carefully thought out. In the absence of some joint effort of this kind there is a very real danger that the hard-earned knowledge of the past may be forgotten. Short cuts are always tempting, and never more so than in times like the present when one discovery follows on the heels of another. No new serum, vaccine, antibiotic, or insecticide can take the place of a healthy stock, a healthy and stable environment, and an adequate state of nutrition.

I began with a definition from Samuel Johnson and I would like to conclude with his answer when asked why he defined the " pastern " as the " knee " of a horse in his Dictionary, for it may serve as an excuse for my shortcomings also. He said, " Ignorance, madam, pure ignorance."

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The Chairman, Professor L. P. Pugh, said it was a great privilege and pleasure to introduce Professor Banks, Professor of Human Ecology at the University of Cambridge. His Department was one of the foremost graduate departments in the Medical School.

Human ecology—the relationship of man to his environment—was a great subject. Professor Banks was a medical man with a long and distinguished career in public health, and had specialised in the broad effects of disease on society and of society on disease. It required little imagination, therefore, to appreciate why Professor Banks had proved such an enthusiastic supporter of comparative medicine within the University of Cambridge, and why the Chairman, for one, was so happy when Professor Banks accepted the Association's invitation to give an address.

Professor Banks then read his paper.

The Chairman said that in some ways it was rather sad that, having heard such a stimulating address, it was not permissible to discuss it. Time and custom did not allow. Nevertheless, it would be the wish of everyone present that he should express deep appreciation for the very careful work which so obviously had been put into the preparation of the address, appreciation for the felicitous terms in which Professor Banks, as a medical man, had drawn attention to the advances in veterinary science during the comparatively recent years, and appreciation for support of the thesis that there was but one medicine, for the problems under investigation were common to men and animals. Finally, he expressed deep appreciation for Professor Banks' contention that the focal point for the two professions in the future, especially in regard to research, must inevitably develop more in the universities which had veterinary and medical schools working side by side in collaboration.

The vote of thanks was carried with acclamation.

Studies of the Normal Animal in Relation to Disease

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IT is a sound and safe policy for any layman, when he undertakes to address a professional audience such as this, to stick to broad principles and to avoid as far as possible detailed discussion. If in addition he can confine his address largely to speculation on future trends, he may avoid criticism and even achieve some minor posthumous reputation. Someone is certain to notice in years to come that one of his prophetic statements bears a passing resemblance to what has indeed happened. For these good reasons, this paper deals with future developments in veterinary science and does so in the most general terms.

For many years, and particularly during the last 10, it has been my good fortune to watch the fight of veterinary science against disease from a ringside seat, or perhaps it would be more correct to say that I have been "in the corner" during some of the battles.

Veterinary science has, over the last 3 decades, a remarkable list of victories to its credit. Many diseases which were ravaging our flocks and herds when the First World War ended have been eliminated or controlled by improved methods of diagnosis, followed by the application of preventive measures and of curative treatments. Others have been extensively studied and there is every hope that they, too, will soon be added to the list of successes. A closer examination of the successes of veterinary science shows, however, that a very large proportion of these have been gained over diseases where a causative organism can be identified which gives rise within a limited time to clearly recognisable symptoms, varying only in their severity, in all the animals infected. The approach has followed broadly the same lines in each instance; first, proof that the disease is transmissible; then the isolation of the responsible organism or the development of a test by which it can be precisely identified; the search for a suitable vaccine or, where this has not been successful, the elimination of infected animals to prevent the spread of the disease. The workers involved in this form of attack are primarily the bacteriologist, the virologist, the histopathologist, and, perhaps to a lesser degree, the parasitologist.

If a list of the most serious diseases of farm animals made in, say, 1920 were compared with a similar list to-day, it would be immediately obvious that the place of first importance, which had been previously occupied by the many transmissible diseases now under control, has been taken by two new groups.

In the first of these groups the disease is still caused by an invading organism, but the symptoms do not necessarily follow within a limited time, nor may they develop at all in many of the infected animals. This group may be illustrated by Johne's disease, where the bacillus is known to remain dormant for an indefinite period only to flare up suddenly for no apparent reason. Another example is the condition known as scrapie, where no organism or other agent has yet been identified and where rarely more than half the sheep, and often far less than this proportion, develop symptoms of the disease after they have been experimentally inoculated with a preparation of the brain of an infected animal; and nothing is known of the mode of transmission of the disease in natural conditions. In the diseases of this group it would appear that a second factor must be present before the organism can become actively pathogenic.

In the second group there is no causative agent so far as we know. An animal becomes ill either for no apparent reason or following exposure to some abnormal condition such as unaccustomed heat or cold, or to a changed diet or during some physiological stress such as parturition.

One or only a small number of animals from a herd which, so far as can be judged, have all been treated in the same way will develop this type of disease. It is easy to give a long list of disorders of this kind—acetonaemia and bloat in cattle, pregnancy toxaemia and swayback in sheep, anaemia in young pigs.

With these 2 groups of diseases, which are now assuming so much greater importance, the old methods of attack break down either partially or completely at the very beginning. If the condition can be transmitted at all, as with scrapie, its incidence is uncertain and the time of incubation is so long it makes the work enormously difficult. In most examples of these groups the disease cannot be produced at will by any means of which we are aware. Even where a causative organism can be isolated or identified, its introduction into the animal cannot alone produce the clinical symptoms; the presence of some second factor is necessary.

In conditions where there is no obvious invasion by a pathogenic organism, we can sometimes partially define the circumstances under which the symptoms develop. We know that bloat often occurs on rich, leguminous pastures, but it does not always occur when animals graze on such a sward, nor is every animal in a herd feeding together affected. We have evidence that swayback is in some way associated with a deficiency of copper, but all pastures low in copper do not cause swayback, nor do all the lambs on a pasture causing swayback suffer from it.

The Need for New Tactics

If the old methods which have given such good dividends in the attack on transmissible diseases will not serve for the study of the two groups of diseases of which I have been speaking, new tactics must be used. So far we have started with the diseased

animal, observed its symptoms and attempted to recreate them. The path between the pathogenic organism and the observed symptoms has been only of secondary consequence, provided that the same organism gave the same results. The clue to the lines which veterinary science will follow in its future attempts to discover methods for the prevention and cure of these more puzzling diseases may well be found in the recent history of the sister science of human medicine. Up to the time of the First World War, human medicine had followed the path which veterinary medicine has followed between the wars. From 1920 onwards, however, the impact of the work and philosophy of such men as Bayliss, Starling, and Hopkins began to be felt in clinical medicine. It led on the one side to an intensified study of the immediate effect of an invading organism on the normal metabolism of an animal and the chain of events which brought about the final symptoms by which the disease was recognised and, on the other, where no organism was involved, to attempts to find the point at which the normal metabolism was first affected. Put shortly, instead of working from effect back to cause, the medical clinicians began to work forward from cause to effect. This was made possible by the extensive studies which had been carried out in physiology and biochemistry and which had given an adequate, though still only partial, knowledge of the workings of the human body. This new approach to the study of disease was developed by a generation of medical men, who as students had read such books as Bayliss's "Principles of General Physiology" and Starling's "Principles of Human Physiology" and from these had learned to look on physiology and biochemistry not as examination hurdles to be surmounted and forgotten, but as the very foundation on which all their future work in medical science must rest. You are all familiar with the work of Banting and Best, which led to the discovery of insulin and the control of diabetes. Their approach to this problem, and the steps which led to its solution, will serve to illustrate the thesis which I am attempting to put forward.

It is not unfair to say that, until the veterinary courses were lengthened, there were few students who regarded physiology and biochemistry as more than necessary evils. Those who were attracted to a career in research turned naturally to the leaders in the profession who were in the main working in one of the branches of pathology.

A new generation of veterinary students is now emerging with much fuller training in physiology and biochemistry. They will want to carry this knowledge into their clinical practice and into research. Trained workers will therefore soon be available for a great expansion in the study of the two groups of diseases which have so far proved largely intractable, but unfortunately they will find for farm animals that they still lack much of the basic knowledge on which to build; for relatively little is known of the physiology and biochemistry of these animals as the result of direct experiment, and we cannot continue to rely on extrapolation from the cat and the dog to cattle, sheep, pigs, and poultry. We know, of course, of many major differences between the ruminants and the single stomached animals, but there must exist many less-obvious species differences about which we have no knowledge, by no means all of which result from the different digestive systems. Avian physiology and biochemistry is even less well known, and years of patient research will be needed before a reasonable basis for clinical work can be provided.

It may be useful to look more closely at our knowledge of one branch of physiology in relation to farm animals. Changes in the composition of blood and urine have proved of the greatest value in the study of human diseases. It was first necessary, however, to establish normal levels for the constituents of these body fluids. Our knowledge of the composition of the blood and urine of the healthy man or woman is far greater than the corresponding knowledge for farm animals, yet medical science has still much to learn about the normal levels of many of the different constituents and how these vary between individuals and in the one individual with changing conditions, such as age or at different times in the reproductive cycle.

What is Normality?

The first difficulty is to define normality. We are too apt to use the word normal without giving sufficient consideration to what we mean. A calf is spoken of as normal if from outward examination it conforms to a generally accepted anatomical standard. We know that no two calves are exactly alike, even identical twins differ to some extent at birth, but there are certain conventional limits beyond which variation is regarded as abnormality. The pedigree breeders have greatly narrowed these limits in conformation and appearance in an attempt to obtain a race breeding as nearly true for external appearance as possible. Yet we know that within such a race of animals often closely inbred there are marked differences in physiological characters.

When we come to consider the physiological and biochemical characters, we find that compared with the relatively gross anatomical features recognised by the breeder they are not only great in number but also they are not constant in the individual animal, varying with changes in diet and environment, with age and the period in the sexual cycle. The changes in the level of any particular constituent in, for example, the blood of one individual animal may follow a regular pattern depending on a physiological rhythm, or they may be random in character arising from external influences, but so long as the animal remains free from disease and is not submitted to any extraordinary stresses which produce conditions similar to disease, there will be limits between which these variations occur, due to the physiological control mechanism of the body. It is therefore possible to determine the range of variation for the healthy individual.

If this range is determined for a number of apparently similar animals, the results will show marked differences. In one animal the maximum value of the range may be higher, in another the minimum value lower; in one animal the spread of the results may be narrow, in another wide. We

therefore have for any particular series of measurements both variation within the individual and variations between different individuals.

Tables of blood constituents, such as those in Albritton's "Standard Values in Blood," are in general the result of many determinations on different individuals and Albritton regards as normal those values within which 95 per cent. of the population lies. There can be no doubt about the importance of such tables, but they require careful interpretation. It is improbable that the full range of variation will be found in one individual, since this range is built up of determinations from those with high average values and those with low; the ranges of the individuals will overlap but not necessarily coincide. It follows, therefore, that the level of a particular blood constituent measured for an individual, whilst falling within the normal range given in a table derived from many individuals, may still be abnormal for the man or animal under examination.

Albritton, in building up his tables, as I have said, used for the criterion of normality the range within which values for 95 per cent. of the population fall. Any individual with a value falling outside this range is regarded as a deviate from the normal.

If, however, we consider the large number of unrelated physiological or biochemical measurements which may be made on any animal, it becomes highly probable that for one or more of these the value obtained will lie outside the 95 per cent. range, which is assumed for normality. In fact for some of these characteristics every animal is likely to appear abnormal measured by these standards. Such a deviation, whether of genetic or environmental origin, may, of course, not affect the animal during its life, either because the abnormality is not in itself important or because the animal is never placed in circumstances when it becomes so.

Liability to Disease

It would, however, seem reasonable to assume that a marked deviation in some metabolic process may render an animal more liable to suffer from a disease attributable in some way to the disturbance of this process, whether the dysfunction arises spontaneously, or as the result of abnormal conditions of environment, or by reason of faulty diet, or due to the presence of a pathogenic organism which affects some link in the chain of chemical reactions involved.

This point may be illustrated by the wide range of islet tissue in the human pancreas and its capacity to produce insulin. It has been estimated that this capacity shows a tenfold variation in the adult. Those with low values are likely to develop diabetes at some period of life, though they may not necessarily do so; those with high values may suffer from hyperinsulinism.

In the ruminant we have a particularly difficult set of problems, in that in addition to the metabolic processes taking place in the animal itself we have to take into account the complex microbiological reactions affecting its food supply. Every practising veterinarian is only too well aware of this, but from time to time it appears to be forgotten in the study of bodily dysfunction. In discussing problems of this type, there is often a tendency to over-simplify them by assuming that what goes into the mouth of a cow or a sheep is necessarily absorbed into its blood stream, either in the form it is fed or, alternatively, by conversion into a particular form which the animal needs. A change in the composition of the microflora of the rumen, or the stimulation of one group of organisms at the expense of another, may well so alter the actual nutrient intake of the animal as to provide the condition of stress needed to give rise to symptoms of disease in a particular animal which exhibits an abnormality in one of the metabolic processes in which the nutrient is involved.

To sum up, what I have attempted to say is that in order to study many of the most serious present-day diseases in farm animals we must know the normal physiological and biochemical processes which are upset when one of these diseases attacks an animal. We know far too little of these processes in healthy farm animals and hence the work of the clinician will be retarded until the physiologists and biochemists can fill in at least the major gaps in our knowledge.

The problems are made more complex by the difficulty in defining normality. Not only is there an inter-individual variation, but the intra-individual variations are also wide. Tables based on the observed range of these variations in a large percentage of the population are only a general guide. A value within the accepted normal variation may well represent an abnormal condition in the individual from which the sample was taken. Equally, many apparently healthy individuals will prove on examination to be abnormal in that some physiological or biochemical characteristic differs materially from that found in the great majority of the population. Whilst these abnormalities do not necessarily result in disease, there is evidence which makes it reasonable to suppose that their presence predisposes the animal to disease.

The Next Clinical Developments

Earlier in this paper I have ventured to suggest that the next developments in veterinary clinical medicine will come from studies of the precise way in which the functioning of the body of a diseased animal differs from the normal physiological and biochemical processes. You may well ask, as the result of what I have just been saying: "Are there in fact any normal values against which those found in a diseased animal can be assessed? Is not every animal an individual and hence unless we know all about a particular animal in health how can we say with certainty what part of the mechanism of its body is functioning abnormally in disease?"

The answer to these questions is that we cannot hope to define any one of the many biological processes making up the animal organism in the precise terms we could use for a chemical reaction in the laboratory. Taken in isolation, each process may, indeed, be a chemical reaction; sometimes relatively simple, more often complex, but in the animal no process can be considered in isolation. Each is related more or less closely to many others. Again, these

chemical reactions are influenced by the physical conditions under which they are taking place. The rate of physical absorption, for example, of the end product from solution controls the speed of reaction; the selective uptake of the reactants on a membrane may enormously increase it. In the healthy animal this interlocking of many chemical reactions in different physical environments forms a complicated self-regulating mechanism. When one reaction is threatening to go too far, another steps in and rights the balance. How far each reaction can go before it is checked will vary from individual to individual. Where the checking mechanisms come into operation late, *i.e.* when concentrations are very high or low, there is clearly a smaller margin of safety. The driver with a slow reaction time may drive for a long time without an accident, but he is in every emergency nearer a crash than one who acts quickly.

So long as this self-balancing mechanism is working the animal may in general be termed healthy; it is when due to some stress—the invasion of a pathogenic organism, a change in diet or physical environment or some physiological climacteric—the self-balancing mechanism no longer works that one or more often a group of the chemical reactions gets out of hand and we say the animal is diseased.

Because we so often use chemical or physical measurements in studying the functioning of the animal organism, and still more because we can make these measurements with considerable precision, we are too often apt to assume that we are obtaining an equally accurate picture of the function of the organism. Chemical and physical measurements are no more than signposts and must be used as such.

The physiologist and the clinician will use them in quite different ways. The former will try by making as many measurements on healthy animals as possible to provide a picture of the normally functioning organism. His objective is to produce a composite picture built up from the many individual pictures he obtains as he carries out one experiment after another. It is like placing a series of semi-transparent images of objects varying slightly in shape one on another until there appears a central dark outline which can be said to represent the average outline of them all. Round this dark outline will be blurred edges where the individual shapes overlap and fall outside.

The clinician works in the opposite way. He is primarily concerned with a sick animal. If, however, he has the research worker's composite picture, he can see where the animal he is treating varies from the average outline in any particular respect. He must, however, have in mind that if the divergence from the normal is only slight it may well be an individual peculiarity. If it is great then it is more probably the cause or an effect of the disease. It is particularly useful to him to study two or more related reactions; if the changes in the one result in the normally expected changes in the other, then there is presumptive evidence that the animal is healthy.

As the clinician's knowledge increases he will know that certain general symptoms which he has learned to recognise are connected with abnormalities in the animal organism, and from this he in turn will build up his own composite picture of an animal suffering from the disease he is studying. As this picture develops, he will see more and more precisely where the diseased animal differs from the normal—the central dark outline for the diseased animal will be a distorted form of the healthy image—and these differences will in the end lead him to the fundamental cause of the disease and so to its treatment and cure.

Encouragement of Research

It is because of the belief expressed by leading veterinarians that only by gaining a fuller knowledge of the physiology and biochemistry of farm animals can we learn how to prevent and cure many of the most serious diseases of our farm animals that the Agricultural Research Council established the Institute of Animal Physiology at Babraham. It is for the same reason that the Council has encouraged, amongst others, the work of Phillipson and Synge at the Rowett Research Institute, of Folley and Kon at the National Institute for Research in Dairying, of Blaxter and Findlay at the Hannah Dairy Research Institute, of Mann and his colleagues in Cambridge and of Elsden's Unit of Microbiology in Sheffield. Many of the investigations carried out in these Institutes and Units may seem at first sight to have little immediate connexion with the work of the veterinary clinician, but they are all directed to filling in the details of the picture of the healthy animal. Although it is the blurred edges of the physiologist's composite picture which are of greatest interest to the clinician, these areas become apparent only when the dark central area of normality has emerged.

In order to study the metabolism of a diseased animal with the detail necessary to establish the respects in which it differs from that of the healthy, it will be essential to hold many sick animals in hospital over long periods. No farmer wishes to keep an animal which no longer gives an economic return, nor is the farm the place to carry out the many detailed tests which will be necessary. In this respect the veterinarian is at a disadvantage compared with his medical confrère. The latter has hospital beds at his disposal in which patients can be studied and long and expensive treatments tried. The cost of maintaining the hospital, the nursing, feeding, and general care of the patients does not fall on the medical school nor, in general, does the cost of treatment. Hospitals, too, have extensive pathological services which can make large numbers of routine tests for the clinician.

The hospitals connected with the veterinary teaching schools are very small compared with those associated with the big medical schools, and a very large part of the cost has to be borne by the university veterinary department. Owners of pets are prepared to pay for their treatment, but with very few exceptions the farmer will not meet hospital costs for any of his stock. Where a disease is to be studied which can be produced at will, the veterinary research worker has to buy his larger animals at a high cost, maintain them himself, and get only the knacker's price for the carcase, if he is lucky enough not to

have to pay to have it destroyed. In diseases where the veterinarian has to collect his sick animals from farms, he may buy them at slaughter price, but he must meet all the cost of keep, care, and treatment. The Agricultural Research Council has at Compton probably the best large-animal hospital facilities in the world, and to some extent these have been used by workers from the veterinary schools for large-scale animal experiments and the Council hopes to continue to help in this way. The animal compound at Compton cannot, however, replace the need for similar accommodation on a smaller scale at the veterinary schools with the necessary funds for their upkeep. These are a university responsibility and the Agricultural Research Council, however willing it may be to help veterinary work in the universities, is not given the funds nor authority to meet the basic costs of upkeep of veterinary hospitals in the teaching schools. All the Council can do is to assist new and promising work with relatively small *ad hoc* grants. I know that funds are short in the early years of the new university quinquennium, but I would plead that the universities, having undertaken veterinary education, should not deny the teachers in the veterinary schools the basic requirements for research without which the instruction will become sterile; and the developments in the control of disease of incalculable value to the farmer which I have tried to foreshadow will come all too slowly through lack of well-trained and inspired young workers.

The Chairman, Mr. J. N. Ritchie, said that Sir William Slater was well known to them all as Secretary of the Agricultural Research Council, an onerous post which he had held for several years. Without more ado, he would ask Sir William to deliver his address.

At the conclusion the Chairman thanked Sir William for a most stimulating paper which forecast some of the progress necessary in their studies of the control of diseases other than those to which Professor A. L. Banks had addressed himself. That was timely, as they had already exploited the results of research already available and must go on to deal with other problems which would cause very serious loss to the farming community if not solved. The papers delivered at that day's plenary sessions were complementary and they were all extremely grateful to Sir William for carrying the story on into the future.

Respiratory Diseases of Sheep

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Introduction

PNEUMONIA must be classed as one of the most important clinical syndromes in sheep, both as an acute killing disease and in a more cnronic form where loss is less apparent.

Pounden and his colleagues (1955) working in Ohio examined 541 apparently healthy sheep at the abattoir and found 15.9 per cent. with definite lesions of pneumonia.

In this country in the course of 400 consecutive sheep *post-mortem* examinations carried out by the author and his colleagues in Northumberland, 15 per cent. were found to have pneumonia.

There are three specific types of pneumonia known to occur in Great Britain; parasitic broncho-pneumonia, enzootic pneumonia, and jaagsiekte. In addition, it is common to find severe congestion of the lungs with bacterial invasion in animals which have been made recumbent by some other primary disease.

Parasitic Broncho-pneumonia

Incidence

In the examination of 3,971 sheep lungs from various parts of England at an abattoir, Rose (1956) found 3,952 (99.5 per cent.) with lungworm lesions. 310 lungs were examined closely, revealing *Muellerius capillaris* in 293, *Cystocaulus ocreatus* in 22, *Dictyocaulus filaria* in 10, and *Protostrongylus rufescens* in two. These figures are probably a good indication of the general incidence of lungworm infestation and of the distribution of the different lungworm species in the sheep population of this country.

Despite the fact that nearly all sheep are infested with lungworms it is uncommon to find large numbers at *post-mortem* examination, and the incidence of clinical disease is low.

Heavy infestations of *D. filaria* occasionally cause parasitic bronchitis. The disease is seen most frequently in weaned lambs on lowland pastures during late autumn and is then often associated with parasitic gastro-enteritis. Apparently sheep can carry heavy infection of *M. capillaris* without showing clinical signs at all, though a considerable amount of lung tissue is rendered inactive and such infestations must impose some strain on the animal.

Diagnosis

Post-mortem examination is the only reliable method. Clinically the condition is more chronic than enzootic pneumonia, and it is usually less chronic and occurs in younger sheep than jaagsiekte. More sheep are affected at the same time than in either of these diseases. Faeces examinations for larvae are very unreliable.

Control and Treatment

There is no proved specific treatment. Limiting the incidence of the disease by husbandry methods is the best policy. Only flocks managed semi-intensively on fixed grazings are likely to be severely affected.

In fold systems, moving the sheep once a week is sufficient to prevent any dangerous build-up. When sheep on fixed grazings have become severely affected, it is usually necessary to treat them for intestinal worms, to give supplementary feeding, and to separate and house the very sick. These nursing measures are probably more effective than any known therapeutic treatment. There are as yet no published records of the use of diethylcarbamazine or the other more recently introduced drugs. Killing slug and snail intermediate hosts on the pastures is rarely necessary, practical, or economic.

Enzootic Pneumonia

This is the most important of the sheep pneumonias to the practising veterinary surgeon because the condition is acute, mortality is high, and differentiation from the other acute killing diseases is of practical importance in control measures.

There is much justification for the use of the term " Pasteurella pneumonia," but to support this contention it is necessary to consider Pasteurella infections in general, together with the various theories which have been advanced supporting a virus origin. An organism first described as *Pasteurella haemolytica* by Newsom and Cross (1932) can be readily isolated in pure culture from the consolidated lungs of nearly all cases of acute pneumonia. This organism differs markedly from *Pasteurella septica* in its low virulence for laboratory animals, its production of haemolysis on blood agar and in some biochemical reactions. *Past. septica* is occasionally isolated from sheep, but its occurrence is comparatively uncommon and it is rarely implicated as a primary cause of pneumonia. The rôle of *Past. haemolytica* as a primary pathogen has been questioned because of its low virulence for laboratory animals and sheep. Thus, only occasionally will 0.5 ml. of a 24-hour broth culture kill mice when given by the intraperitoneal route, and strains are rarely virulent for any other laboratory animals. Montgomerie, Bosworth and Glover (1938), using various routes and methods, failed to infect at least 10 sheep (usually adult sheep where stated) with freshly isolated strains of *Past. haemolytica*, but they did induce severe pulmonary changes, though not the typical disease, by intravenous and intrapulmonary inoculations of suspensions of affected lungs. On the other hand, Dungal (1931) in Iceland successfully infected three adult sheep by intratracheal injection of a nine-

hour culture and produced severe and typical lesions. This strain showed the same lack of virulence for laboratory animals and was subsequently typed serologically by Montgomerie *et al.*, and found to be identical with one of their two main types. More recently, Stamp, Watt and Thomlinson (1955), working on septicaemia in lambs associated with *Past. haemolytica*, were able to kill five out of eight lambs by the intravenous or subcutaneous inoculation of cultures. Whilst the disease they were investigating was as often septicaemic as pneumonic in form, they emphasised the importance of the work in assessing the pathogenic significance of the organism in pneumonia. In attempting to determine the lethal dose, they encountered considerable variation from one sheep to another and also considered that susceptibility decreased with age. Such factors could account for the varied results obtained by Montgomerie and his co-workers.

Additional support for the rôle of *Past. haemolytica* as a primary pathogen is provided by a consideration of routine *post-mortem* examination records. Thus, in the examination of 66 consecutive cases of pneumonia in sheep over three months old at the Newcastle Veterinary Investigation Centre, *Past. haemolytica* was isolated 61 times and was present in pure culture on 55 occasions. Similarly, at the Penrith Veterinary Investigation Centre, only 19 of 88 consecutive cases of pneumonia showed organisms other than *Past. haemolytica* (Health, 1957, private communication). It would appear likely that if the primary agent was a virus or other organism, the proportion of isolations of *Past. haemolytica* would be lower and the flora of the infected lung more varied.

Conversely, in the bacteriological examination of 17 sets of pneumonic lungs by the author at the Cambridge Veterinary Investigation Centre where subsequent histological examinations showed the presence of lesions typical of jaagsiekte, *Past. haemolytica* was never isolated. A few streptococci and staphylococci were present in three lungs received in a decomposing state. During the same period and from the same farm, three sheep were received showing typical enzootic pneumonia, and from their lungs profuse pure cultures of *Past. haemolytica* were readily isolated. There were no gross or histological changes resembing jaagsiekte in these lungs.

If *Past. septica* were a common secondary invader of sheeps' lungs, it would be expected frequently in the later stages of jaagsiekte, particularly when it is known to exist in other stock on the same farm at the same time.

It has been suggested that *Past. haemolytica* is frequently present in healthy sheep. Bosworth and Lovell (1944) were able to isolate a similar organism from nasal swabs of half of the sheep in both an infected and a recovered flock. However, routine cultural examinations of the upper trachea of sheep received at the Cambridge Veterinary Investigation Centre have shown the presence of the organism in six of seven sheep showing enzootic pneumonia, but only one of the 18 which died of other causes. *Past. haemolytica* has never been isolated from non-consolidated lungs of sheep dead of other causes or even non-consolidated areas of pneumonic lung associated with Pasteurella. It seems probable that the organism can exist in the upper respiratory tract of healthy sheep, but its occurrence in lung tissue in quantity is very constantly associated with pneumonia.

It has been suggested that a virus is involved in the production of enzootic pneumonia, but no definite evidence has yet been produced in this country. There are, however, reports from other countries suggesting the occasional occurrence of viruses in the lungs of sheep. In 1946, Marcos, Zaki and Zaki in Egypt transmitted a pneumonic disease to rabbits and sheep using blood filtrates. It is not, however, made clear whether the disease they were investigating was identical with the enzootic pneumonia encountered in this country, and some lesions they describe are most markedly different. Full details of their techniques are not always given and a repetition of their work is most desirable.

Ramirez, Gray and Thorpe (1952) in Michigan isolated and passaged through 19 chick embryos a virus which gave pneumonic lesions in the embryo and marked pocks on the membranes. Their isolation was, however, from only one set of bacteriologically sterile lungs and no attempt was made to re-infect sheep with the material. Pokerny (1955) in Czechoslovakia passaged an organism in chick embryos and reproduced pneumonia in two lambs by intranasal installation. On this evidence he claimed that the organism, called by him *Pasteurella oviseptica*, is only a secondary invader.

Summarising, the evidence at present available would suggest that *Past. haemolytica* is the most important organism known to be involved in enzootic pneumonia though susceptibility varies greatly from one sheep to another and with age and other factors. Environmental changes are probably the most important of the latter, but it seems unlikely that a virus is commonly involved in this country.

Incidence

Whatever the differences of opinion as to its true cause, there is little doubt that a disease associated with *Past. haemolytica* exists in characteristic clinical form in many parts of the world. Descriptions have been given of the disease in England, Wales, Scotland, North America, Iceland, South Africa, Japan, Russia, and Switzerland (Montgomerie *et al.*, 1938; Campbell, Campbell & Dromney, 1949; Marsh, 1953; Dungal, 1931; Henning & Brown, 1936; Ochi, 1933; Poluikovski & Alikaer, 1954; Dolder & Leuenberger, 1948). Peculiarly enough, only one slight outbreak has been described in Australia (Beveridge, 1937).

Clinical Picture

Enzootic pneumonia is the commonest form of acute fatal pneumonia encountered in routine *post-mortem* examinations in all areas of Great Britain. There is a marked seasonal incidence, most losses occurring in March and April, or September and October.

Frequently sudden deaths are the first sign of trouble. Closer attention and rounding up then reveals excessive coughing in the flock with some

mucoid discharge from the nostrils. Spasms of convulsive coughing are characteristic. In advanced cases the animals stand apart and show marked respiratory efforts. The temperature is usually only slightly raised. The period between the appearance of symptoms and death varies considerably from a few hours to a week, but the general recovery rate is high. Mortality rarely exceeds 15 per cent. of the flock and is more frequently about 5 per cent. There is, however, considerable loss in condition in survivors. Young lambs are not often affected, though an allied septicaemic condition occurs in lambs in Scotland and has been described by Stamp *et al.* (1955). Losses are frequently associated with the gathering of hill ewes into confined pastures as for feeding in very bad weather. Any close gathering such as transport in closed trucks during hot and humid weather appears to be especially predisposing. Sudden changes in temperature and the direction of the wind are also often associated with an outbreak.

Post-mortem *findings*

These are usually confined to the thoracic cavity and often consist of lung consolidation only. The apical and cardiac lobes are most frequently involved, but it is rare for more than a third of the total lung tissue to be affected. The affected tissue has a characteristic blue-grey colour and is very solid resembling liver tissue. Occasionally there is a slight pleurisy and/or pericarditis. General subcutaneous haemorrhages are frequently present.

The histological appearance varies from area to area. All stages of acute inflammation are seen from general congestion of the lung tissue and inflammation of the bronchi to necrosis and catarrhal changes in the alveoli and bronchi filled with cellular exudate.

Bacteriological findings

Microscopic examination of impression smears of cut consolidated lung shows many small gram-negative organisms which, however, only occasionally show bipolar staining. Inoculation on to blood agar regularly produces an abundant growth of small, round, raised, shiny colonies after 24 hours' incubation, showing a narrow zone of haemolysis in blood of all the usual species.

In freshly dead carcases, the organism is usually isolated in pure culture from the consolidated lung, but most attempts to isolate the organism from macroscopically healthy lung tissue in the same animal have failed. Only occasionally it is present in the mediastinal lymph glands, heart blood, liver, and spleen when the condition merges with the septicaemia described by Stamp *et al.* in young lambs.

Microscopic examinations of primary cultures show a short gram-negative rod which is frequently joined into wavy filaments. There is no bipolarity.

Confirmatory tests which can be used in routine laboratory diagnosis and which distinguish the organism from other members of the group are tabulated below. The organism dies in a few days on blood agar at room temperature, but survives for a few weeks in Robertson's cooked meat medium.

DIFFERENTIAL TESTS

Pasteurella species	Haemolysis	Indole production	Growth on MacConkey media	Pathogenicity to mice
Past. haemolytica	Narrow zone	–	Slight	–
Past. septica	–	+	–	+
Past. pseudotuberculosis	–	–	Slight	–

Method of Spread

The inability of the organism to survive in the laboratory would suggest that it is perpetuated by apparently healthy carriers. Bosworth and Lovell (1944) isolated an apparently identical organism from the upper respiratory tract of about half the animals in both a recovered and an infected flock. The author's experience at routine *post-mortem* examinations has not yet confirmed this high incidence, but Bosworth and Lovell suggest that the number of isolations are related to the diligence of the search, which continues. Dungal (1931) in Iceland examined the noses of shepherds and sheep dogs without detecting any carriers. *Oestrus ovis* was once thought to be implicated in the transmission of the disease, but there is no evidence to support this theory.

It seems most probable that the organism survives in the upper respiratory tract rather than the lungs of apparently healthy sheep which act as carriers. Gathering together for any reason leads to closer contact between susceptible and carrier sheep, and over-heating, increased respiratory rates, and temperature changes would then be more likely to lead to clinical cases.

Control and Treatment

Attention to the suspected precipitating husbandry factors are obviously of prime importance. Overcrowding in trucks, long journeys by road, transport in hot or humid weather, rough or hurried handling, and close gathering should be avoided. Adequate trough space should be provided. Stamp *et al.* found that deaths frequently ceased after a change to poorer pasture, and even recommended gathering into pens for the night which is partly contra-indicated by the above. The *Sheep Handbook of the British Veterinary Association* (1955) recommends leaving pastures free for some time after an outbreak, but it seems unlikely that the organism or even a postulated virus would survive sufficiently long on pasture to be of practical importance.

Past. haemolytica shows maximum sensitivity *in vitro* to chloramphenicol, which is theoretically the treatment of choice. However, treatment is not possible in peracute cases and is probably economically prohibited for other cases on a flock basis. The overheating and excitement associated with any form of drenching are risks hardly justified by the effect of any other known medicine.

Vaccines have been recommended, and commercial products are at present widely used in parts of Scot-

land. Dungal (1931) carried out a small trial using a dead vaccine which promised well, but no controls were kept. Dolder and Leuenberger (1948) prepared an autogenous vaccine which gave good results under field conditions, but their method of preparation is not described. The authors' experience with formolised autogenous vaccines has been promising. The organism freshly isolated from the flock was grown in litre quantities of Lemco broth for 24 hours. Formalin was added to a final strength of 0.5 per cent. and the mixture re-incubated for 24 hours, bottled, and tested for sterility. A single subcutaneous injection of 5 ml. was given to each sheep. In 14 outbreaks treated, all losses ceased shortly after injection, but in only three flocks were adequate controls left, and in only one of these flocks did losses continue on a significant scale in the control group after the time of inoculation.

The estimation of the value of any vaccine treatment in field cases is not only hampered by the usual difficulties of leaving sufficient controls, but the frequency with which an outbreak suddenly and completely disappears. Vaccines are a most promising line of control, but it would be most valuable at this stage if artificial laboratory infection of sheep with *Past. haemolytica* could be regularised sufficiently to assess some of the factors involved. To determine, for example, if an autogenous strain of vaccine is necessary, the best route and course of injection, and how long an effective immunity might be expected to persist. Field trials could then be better planned and would be likely to prove more fruitful.

Adjuvant vaccines containing mineral oil and alum have been used for bovine Pasteurella infections with good results and would be well worth trying in this condition (Vancheswara Iyer, Gopalakrishnan & Ramani, 1955).

Jaagsiekte

Robertson (1904) described a fatal disease of sheep in South Africa, characterised by coughing and emaciation. When driven hard, advanced cases would fall exhausted which gave rise to the name "jagziekte" from the Dutch "jaagen" to drive, and "ziekte" a disease. The name was later evolved to "jaagziekte" in which "jaag" is Afrikaans. Now the Afrikaans spelling of the word is usually "jaagsiekte" and this form has been widely adopted and is used in this paper.

Cowdry (1925) studied the pathology of the disease in South Africa, and suggested that the condition was very similar to that described by M'Fadyean as verminous pneumonia in sheep in 1920. M'Fadyean himself (1938), referring back to both his 1920 paper and an earlier paper on verminous pneumonia in 1894, concludes that some of his cases were, in fact, jaagsiekte. There is, therefore, evidence to suggest that the disease has existed in this country throughout this century. Cowdry and Marsh (1926) reported a progressive pneumonia in sheep in Montana, U.S.A., indistinguishable from jaagsiekte. In 1938, however, interest in the disease was aroused by its occurrence in epizootic form in Iceland (Dungal, 1938) where the disease was apparently introduced by sheep imported from Germany. A very high incidence in the Icelandic sheep was attributed to the necessity of housing large numbers together during the winter season.

Incidence in Great Britain

Following M'Fadyean's reports in 1894 and 1920, there are no records of the disease in this country until Blakemore and Bosworth (1941) described an outbreak in Norfolk. Harbour and Jamieson (1946) described two outbreaks in Berwickshire and Aberdeenshire, Scotland, and there are many reasons to believe that the disease is well known in central Scotland at the present time. A further outbreak in Norfolk, but apparently in no way connected with that described by Blakemore and Bosworth, has been under investigation by the author and his colleagues since 1956. Loosmore (private communication, 1957) has investigated an outbreak near Reading, and the disease was diagnosed recently in the south-west of England (Fincham, 1957). In all reported cases the source of infection appears to have been sheep purchased in Scotland.

Clinical Appearance

There are close similarities between those outbreaks already described and the outbreak at present under investigation in Norfolk; this will therefore be described in some detail.

Two flocks each consisting of 300 "Scotch greyface" (Scotch Blackface crossed with Border Leicester tups) are kept, and replacements bought as gimmer lambs nine months old in Kincardineshire, Scotland. The gimmers are reared separately and brought into the flocks as shearling ewes. Crossed Suffolk lambs are produced and all sold off in June or as soon thereafter as possible. The ewes are kept as long as possible until "broken mouthed." The flocks were established in their present form in 1951, and during the last three years there have been annual losses approximately equal to 8 per cent. of the total ewes. Most cases of jaagsiekte occurred in ewes three or four years old, but three cases have been confirmed in purchased sheep less than one year old. The youngest was a gimmer 10 months old which had been on the farm for only three months and had no direct contact with the adult flock. There is little doubt, therefore, that the disease has been continuously introduced into the flock by the purchased replacements. The losses quoted include all adult losses, but during the last year all deaths have been examined at the laboratory and more reliable figures of jaagsiekte losses are available.

The first signs noticed are an occasional cough and some panting, usually after being gathered. As the disease advances, the sheep lose condition, the wool becomes coarse and rough, the respiratory symptoms become more marked, the eyes water and clear fluid pours down the nose. By raising the hind legs, up to a third of a pint can be made to pour from the nose and this test is considered diagnostic of the disease by some shepherds. The condition advances in severity

over a period of six week to four months and no clinical cases have been known to recover. The course is very prolonged and most animals are slaughtered for humanitarian reasons. Cases occur at all times of the year. The temperature is rarely raised except in the final stages when secondary infections are common. During the period June 1956 to March 1957, 17 cases were diagnosed by *post-mortem* and histological examinations. Three sheep were newly purchased and less than one year old. The remainder were ewes between three and four years old.

Post-mortem *Findings*

The characteristic lesions were confined to the thoracic cavity. The lungs were greatly increased in size and weight, averaging 9 lb. as compared with a normal weight of 3 lb. There were extensive areas of consolidation, the lower portions and the apical lobes being most frequently affected. There was a great excess of frothy fluid in the bronchi. In four cases which were allowed to die there was also abscess formation and pleural adhesions, and in these cases streptococci and coliforms were isolated on culture. Examinations of the other 12 animals failed to reveal any bacteria in 10, and on no occasion was *Past. haemolytica* isolated. During the same period, however, *Past. haemolytica* was readily isolated from a five-month-old lamb and two ewes showing typical clinical signs and *post-mortem* appearances of enzootic pneumonia, but no macroscopic or histological lesions of jaagsiekte.

Histological examinations showed the characteristic changes in the epithelium of the alveoli where the cells had become cubical or columnar in shape giving an adenomatous appearance.

Aetiology and Method of Spread

M'Fadyean (1894) associated the condition with lungworms, but the investigations of Dungal, Gislason and Taylor (1938) showed that they had little, if any, association with the condition. Though histologically similar to a neoplasm and discussed as such by de Kock (1929), it had been suspected for a long time that the disease was due to a specific virus (Cowdry, 1925). Dungal *et al.* (1938) succeeded in transmitting the disease by housing healthy with infected sheep, and in a series of careful transmission experiments Dungal (1946) was able to show that infection could take place only by the respiratory route and that material remained infective after Gradocol filtration (0.9μ). Transmission was not regular and there were many failures but the disease was transmitted by housing sheep with their heads in close proximity but not by close body contact when the heads were separated. Nor did faeces from infected sheep set up the disease when fed to other sheep. Exhaled air was collected in a glycerine mixture and used successfully as an infective agent by the intratracheal and intrapulmonary routes. Lesions were found about four to eight months after inoculation when sheep were killed for examination, but a natural incubation period would probably be much longer.

This method of spread helps to explain why in Iceland, where sheep are regularly housed indoors during the winter, the incidence often reached 80 per cent. but that in this country, South Africa and Germany the incidence is much lower and has been quoted in Germany as 2 per cent. (Dungal, 1939).

Palsson (1948) studying the disease in Iceland found that losses were greatest during the first two years after introduction into a clean flock, and he suggested that resistant strains may be bred. Observations by the author on the flock in Norfolk have left little doubt that there has been continuous reintroduction of the disease by purchased replacement gimmers but there may well also have been spread within the flock.

Control

No specific methods of control can be recommended at present. The early detection, isolation and elimination of clinical cases is obviously of the utmost importance. In Iceland, where the incidence reached such high levels, it was considered necessary to slaughter all animals in infected areas, and it appears at present that this policy was justified.

Whilst in Great Britain the over-all incidence is so low that there need be no thought of such drastic action, changes to more intensive management methods might lead to a serious increase in incidence. The presence of the disease at all is a potential danger to the export trade.

The ability to transmit the disease makes the study of vaccines possible and it is hoped to pursue this line of investigation in the near future.

Other Pneumonic Conditions

There are several other chronic pneumonic conditions bearing some similarities to jaagsiekte, but they have not been recorded in this country.

A disease known as maedi was introduced into Iceland at the same time as jaagsiekte, which disease it resembles in being a chronic and fatal pneumonia of adult sheep which runs a course of three months or more. According to Sigurdssen (1954) it can be readily distinguished by the lack of the characteristic fluid in the lungs and by the general *post-mortem* picture. The lungs are grey-yellow in colour and grossly enlarged, up to four times the normal weight, but the tissue is softer than normal.

Bouhite is a chronic pneumonia seen in young sheep grazing in pine forests in France. It is believed to be associated with the ingestion of terebinth, either direct from pine needles or more probably from contaminated water. Numerous greyish-yellow nodules 1 to 3 cm. in diameter are found in the lungs and once symptoms have appeared the disease is invariably fatal.

Summary

There are three specific types of pneumonia in sheep known in Great Britain.

Parasitic broncho-pneumonia though widespread is not often clinically serious.

Enzootic pneumonia is the form most frequently encountered and is constantly associated with *Pasteurella haemolytica*. The rôle of this organism is discussed.

Jaagsiekte occurs in England and six outbreaks are recorded all of which have followed the purchase of replacement sheep in Scotland. Infected flocks have suffered serious losses and the disease is a potential danger.

Control measures and future experiments for each type of pneumonia are discussed.

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THE SPEAKER'S INTRODUCTION

Mr. A. J. Stevens, in introducing his paper, said that the paper was prepared as an attempt to clarify a subject not yet well worked out, and to offer such practical advice as could be given at the present stage of knowledge. Perhaps that aim had produced some irregularities which he would endeavour to indicate.

Parasitic pneumonia was very widespread, but he had limited its discussion because he believed that it was comparatively uncommon to encounter it in practice. It was more frequent in the west than in the east of Great Britain, and perhaps he was biased as his own observations had all been made in the east. However, it certainly could not claim the importance of husk in cattle and could only rarely warrant similar methods of control and treatment. Some of the new drugs recently introduced which held great promise might still be uneconomic for treatment on a flock basis.

With regard to bacterial pneumonia, occasionally at *post-mortem* examinations one encountered pneumonia associated with organisms other than Pasteurella; *Corynebacterium pyogenes* and members of the Actinomycete group were not infrequently present. However, they had not been recorded in epizootic forms. Their diagnosis in life was always difficult and treatment most unsatisfactory. Consequently, he had devoted the bulk of the paper to enzootic pneumonia associated with *Pasteurella haemolytica.*

The disease took a well-marked course of such a nature and severity that veterinary advice was frequently sought. A diagnosis could be rapidly made by clinical and laboratory methods and some helpful measures introduced. He felt that there was a future for vaccines, not only to limit outbreaks already occurring, but for the protection of sheep exposed to conditions likely to induce the disease. The use of sulphadimidine* which was justified on theoretical grounds and which appeared to have some beneficial effects in practice should have been mentioned. Controlled trials, however, were almost impossible to carry out. The exact cause of enzootic pneumonia presented an interesting academic problem which was to receive more attention from the opener of the discussion. The author's own view after considering the evidence at present available was that *Pasteurella haemolytica* was of prime significance. The organism which had been isolated from the upper respiratory tract of normal sheep might well be identical with the haemolytic Pasteurella in pneumonic lung and capable of causing pneumonia when suitable environmental conditions occurred.

Perhaps in view of the former remarks there might be some surprise to note that time had been devoted to jaagsiekte. There were several good reasons for that, not least the fact that it had not been widely appreciated that the disease occurred at all in this country. Cases might easily have been overlooked in some flocks because of the chronic nature of the disease and the ready acceptance of an expected annual loss. The incidence was, therefore, probably greater than was known. Only a short time previously the condition was diagnosed in another Norfolk flock. The breed was Greyface and the young stock purchased in Scotland. The incidence might have risen with the introduction of very close folding. The diagnosis of the disease in a breeding flock was something akin to the finding of scrapie and could seriously lower the sale and potential export values. In flocks where the disease was known to exist losses were very considerable. Ten per cent. of the total adults per year had been recorded. The possibility of a situation even slightly resembling that which existed in Iceland should not be ignored. It was felt, therefore, that the attention given in the paper to jaagsiekte was justified, and he would conclude by showing 6 slides illustrating the clinical features and *post-mortem* appearance of this disease.

The Opener

Mr. G. R. Smith said: "I should like to begin by thanking Mr. Stevens and congratulating him on his paper. He has been in a good position to assess many of the general problems associated with sheep pneumonias and has picked out a number of very important points which are worthy of careful consideration. I should also like to say how much I appreciate the invitation of the Organising Committee to open this discussion.

* Sulphamezathine.

"A number of infective agents are, of course, known to be associated at times with disease processes in the respiratory tracts of sheep. Some of these agents show no special predilection for the respiratory system but occur with comparable or greater frequency in disease of other parts of the body, and under this heading we might include such organisms as *Actinobacillus lignieresi, Corynebacterium pyogenes,* streptococci, staphylococci and *Fusiformis necrophorus.* Other organisms such as certain parasitic worms, the agent of jaagsiekte and *Pasteurella haemolytica* show either a complete specificity or a marked preference for lung tissue as a site in which to establish themselves and become pathogenic. It is this latter group that Mr. Stevens has chosen to discuss, and since the only member of which I have any special knowledge is *Past. haemolytica* I propose to confine my remarks to this organism.

"It was first described well over 30 years ago but was not given its present name until some considerable time afterwards. There have been numerous references to it since, or at least to organisms which seem to have been quite similar. There are, however, occasional discrepancies in the accounts given and perhaps we should bear in mind the possibility that all these descriptions may not have referred precisely to the same organism. Some authors have preferred, perhaps wisely, not to use the name Pasteurella. Certainly we should not allow ourselves to forget that there are several important and constant differences between this organism and *Past. septica.*

"From his own observations Mr. Stevens has clearly pointed out the frequency with which *Past. haemolytica* is recovered from sheep pneumonias. He has also mentioned that the work of others in the past has suggested that the organisms may quite frequently be carried in the nasal passages of healthy sheep, a view with which I am in full agreement.

"Low titre agglutinins occur commonly in sheep sera. Using a single strain which was obtained from a lamb septicaemia and which gives satisfactory agglutination in the presence of antisera, all of more than 50 adult sheep tested have been positive. The agglutinating power of lamb sera is less marked and often absent altogether unless incubation is prolonged. These facts should, however, be viewed within the context of what we already know of natural agglutinins. The sera of a number of species including the sheep contain agglutinins to a wide range of bacteria, many of which are not known to be associated with these animal species. (Gibson, 1930; Lovell, 1932, 1934.) As far as *Past. haemolytica* is concerned there is good evidence of widespread incidence of the organism among sheep, nevertheless, it would be unwise to make assumptions as to the mode of origin of these agglutinins.

"The possible rôle of *Past. haemolytica* as a primary pathogen has been discussed in some detail by Mr. Stevens and he has made some very interesting observations. However, as far as sheep pneumonia is concerned, one can say straight away that there is no conclusive evidence whether it is, or is not, a primary pathogen. The typical disease has not been regularly reproduced either by the inoculation of diseased tissue suspensions or heavy suspensions of organisms grown in culture. We should not necessarily despair over this, however. Excluding the more highly invasive pathogens, the whole business of experimental respiratory infection is probably often quite complicated and a number of factors may require careful consideration; such factors as the state of the infecting organism, the method by which it is applied to the animal, the part of the respiratory tree to which it is applied, and the state of the animal at the time of infection. Nevertheless, some would argue that the consistent production of pneumonia using some highly specialised laboratory method would not necessarily mean that *Past. haemolytica* is capable of behaving as a primary pathogen in the field.

"One should perhaps mention here that the failure to set up the disease by inoculation of infected tissue suspensions does not lend any support to the suggestion put forward by some workers that a virus or other inapparent organism may be the primary agent, though neither does it rule out such a possibility.

"It is an interesting fact that secondary bacterial invasion in cases of jaagsiekte is the exception rather than the rule, unless such cases are allowed to proceed to the terminal stages. (Dungal, Gislason and Taylor, 1938.) In the outbreak in two flocks in Norfolk described in Mr. Stevens's paper we read that of 12 typical cases which were presumably killed 10 were bacteriologically sterile. *Past. haemolytica* was not recovered from a single case in spite of the fact that it was present in the flock and causing enzootic pneumonia on a small scale at the same time. Mr. Stevens suggests from this that the organism is probably not a common secondary invader, but I think that one might question this reasoning. Apart from other considerations, one surely should not conclude that all prior infections of the lung must necessarily predispose to a common secondary pulmonary invader. Conceivably antagonisms might occur between particular infections, and examples of this type of immunity where the protection is serologically quite non-specific are not unknown (see Cowan, 1939; North & Anderson, 1942; Henderson, *et al.,* 1956). Thus it could be argued that perhaps jaagsiekte creates conditions in the lung which actively discourage the establishment of *Past. haemolytica.*

"However, it would appear likely that in certain cases a breach may be effected by prior infections. Carter (1956) has given an account of some recent experiments in calves in which he claims to have initiated 8 clinical infections out of 19 calves exposed to *Past. haemolytica* in various ways. His usual procedure was to inoculate calves intranasally with young primary cultures. Often comminuted agar was contained in the inoculum. It appears that some of the calves had been affected with chronic pneumonias (of which a proportion, at any rate, were due to *C. pyogenes*) prior to exposure, and it is of interest that Carter postulated from his results that the production of severe *Past. haemolytica* infections had been facilitated by the pre-existing inapparent chronic pneumonias.

"This organism does, of course, exist sometimes in pneumonic lung tissue in conjunction with other organisms such as *C. pyogenes.* In some such cases the type of lesion and very large numbers of *Corynebacteria* as compared with Pasteurella might tempt one to suspect that the latter were present only as secondary invaders, although one cannot be certain.

"If efficient vaccination against *Past. haemolytica* became possible it might incidentally help to clarify our ideas about sheep pneumonias. If cases do, sometimes at any rate, occur where a primary agent such as a virus is masked by secondary invasion of *Past. haemolytica,* a vaccine which largely prevented invasion of the lung by Pasteurella could be expected to reveal such primary agents if they were capable of producing disease by themselves.

"Leaving aside for the moment the question of the rôle of *Past. haemolytica* as a primary invader in sheep pneumonia, there is little doubt that the organism is of pathogenic significance. Impression smears from pneumonic lungs which subsequently yield pure cultures often show hundreds of bacteria per field. Viable counts on material from 4 consecutive cases gave numbers in lung tissue varying from 300×10^3 to 900×10^6 per gramme of tissue. The mucus present at the base of the trachea in one case contained 75×10^6 bacteria per ml. The pus-like exudates present in the bronchi of 2 cases both gave counts of several thousand million per ml. The method of counting lung tissue would almost certainly have given figures rather lower than the true values. In one of these sheep it was estimated from the viable count and weight of lung tissue involved that the total number of living organisms present would have been roughly equivalent to those contained in 500 ml. of 24-hour broth culture.

"The work of Stamp, Watt and Thomlinson which Mr. Stevens has cited, and which is of particular interest as regards pathogenicity, showed that the septicaemic disease of lambs as encountered in the field could be reproduced by intravenous injection of tissue suspensions or cultures, and that Koch's postulates could undoubtedly be satisfied. The *post-mortem* picture in septicaemic cases is essentially one of congestion, oedema and haemorrhage, and I have noticed that the symptoms include marked respiratory distress and diarrhoea. This is the type of disease that one might expect to result from toxic concentrations of a gramme-negative organism. Intravenous injection of a large dose of killed culture into a sheep has, in fact, been found to produce

similar symptoms, and death with severe haemorrhage. It is interesting also that in some cases of pneumonia the same types of lesion have been reported in parts of the body other than the lungs (Montgomerie, *et al.*, 1938; Campbell, *et al.*, 1949). Petechiation of the sub-epicardial surface of the heart is sometimes especially marked.

"In the published work on experimental septicaemia death almost always followed lethal intravenous inoculations within the short period of 12 hours, and the doses used were probably rather large, so that possibly after only a few bacterial generations a toxic level would have been reached and the animals' fate sealed. There is some doubt as to whether doses which would generally be considered small or smallish would, in fact be capable of producing death, at any rate in what we look upon as normal animals. The position may be different in animals whose resistance is lower than average, due either to some particular stress or to some intrinsic factor, or both. If not, then we shall have to offer some explanation as to how such large numbers of organisms find their way into the system in naturally occurring disease.

"We must not forget the possibility of increased virulence of the organism itself. The field evidence would tend to suggest, however, that if this does occur it is probably of relatively little importance. Environmental predisposing causes would seem to play a bigger part, and certainly in the case of septicaemias it has been pointed out that a change back to poorer pasture will usually check the disease at once. Again, the fact that the pneumonia is not reproduced experimentally by intratracheal or intrapleural injections of diseased tissue suspensions or primary cultures would tend to suggest that if any enhancement of virulence does occur, it is certainly not a factor of overwhelming importance.

"As regards their pathogenicity, the strains found in the nasal passages of normal sheep have not been found to differ from strains isolated from cases of disease. I have found them equally capable of producing true infections in mice by the methods which I shall mention later, and I am told by Dr. Watt that he has found them equally capable of producing septicaemia and death in sheep. One might be tempted to assume, therefore, that the portal of entry in disease is the respiratory tract, and such may indeed be the case. Nevertheless, the possibility of blood-borne infections of the lung originating from some other site cannot altogether be ruled out. Stamp, Watt and Thomlinson have stated that in septicaemic cases there is no histological evidence that the primary site of invasion is the lung, and furthermore in several cases where some frank pneumonic lesions were present they were considered secondary to bacterial thrombi in the pulmonary vessels.

"Perhaps I might mention at this point the results of some unpublished work done by Dr. McEwen which seems to me to throw some light on the pathogenicity of this organism and at the same time to give rise to further difficult questions. Dr. McEwen first established that *Past. haemolytica* given by mouth to sheep could, in certain individuals and under certain circumstances, be recovered from the abomasum and small intestine. He then carried out a group of experiments to see if large doses of organisms given orally could produce death of the animal. Of 47 lambs maintained on various types of diet and receiving different types of suspension of *Past. haemolytica* 12 died, usually within 24 hours. Of these, 7 died from a septicaemia, while 2 yielded organisms from the lungs only. Three showed no specific lesions and yielded no organisms on culture. A very interesting feature is that in spite of a number of subsequent attempts these results could never be repeated.

Mr. Stevens has mentioned that the rôle of *Past. haemolytica* as a primary pathogen has been questioned, partly because of its low virulence for laboratory animals. Certainly the dose necessary to kill mice by intraperitoneal inoculation is of the order of hundreds of millions of viable bacteria, which is in no way comparable with the small dose which will suffice for a frankly invasive organism. Probably death results in part from toxicity and in part from multiplication. True infections can be established in mice by two methods. In each of these a greatly reduced dose may be used and marked multiplication occurs.

"The first method is by intracerebral injection, and in this case an adequate dose will produce death within 10 days from an infection which is confined to the brain and meninges. The LD_{50} for all strains examined so far would appear to be in the low thousands. The second method consists of the intraperitoneal injection of organisms together with hogg gastric mucin, and this results in a rapidly fatal septicaemia. Gastric mucin has lowered the resistance of mice to all strains tested so far, though to a greater degree with some than with others.

"Each of these two methods of infection has been proved capable of demonstrating passive protection by certain immune sera obtained from sheep, and this in itself suggests several possibilities for future research. In the first place one hopes that it will provide a means of investigating some of the problems involved in artificial immunisation so that the selection of vaccines for field trials may be put on a more rational basis. Work on these lines has begun and the use of adjuvants as mentioned by Mr. Stevens is included in the study. In the second place there is a reasonable prospect that these protection tests will be useful in epidemiological studies. We have no information at present as to levels of protective antibody in various types of sheep population, and such information might give us a better insight into some of the problems associated with *Past. haemolytica* infections."

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The General Discussion

Dr. J. A. Watt (Edinburgh) said: "The disease is not common in south-east Scotland, only 2 outbreaks having been seen in 3 years. The Scots Greyface lamb in which Mr. Stevens's cases occurred is bred from the cast Blackface ewe. As the disease occurs chiefly in young ewes it does not appear that the lambs are likely to have contracted it from their mothers. As a patriotic Scot might I suggest that the high incidence in Mr. Stevens's outbreaks was the result of introducing fully susceptible lambs to an environment where the disease is endemic?

"With regard to the pneumonias associated with *Pasteurella haemolytica* I would like to know what importance Mr. Stevens attaches to environmental and management factors? As we see the disease in Scotland it is very common amongst cast Blackface ewes brought to arable farms for lambing and in hill ewes lambed in the inbye land. The epidemiology suggests that these changes in habitat may be important predisposing causes to the disease."

Mr. Graham T. Marr (Inverness) said: "Jaagsiekte, or a condition that we normally diagnose as jaagsiekte, is widespread in the North of Scotland, but the disease is nearly always sporadic. *Pasteurella haemolytica* has been recovered from cases of jaagsiekte but this is the exception rather than the rule.

Pasteurella pneumonia is well known in the area and can be very troublesome. It frequently occurs in ewes in the spring and summer and in hoggs during the winter. *Past. haemolytica* infection has been found to be the cause of death of 2-day-old lambs. In one case of this kind many of the ewes were affected with a clinical pneumonia and nasal swabs from all the ewes sampled yielded *Past. haemolytica*. Deaths in the lambs stopped after they were inoculated with a commercial serum which agglutinated the Pasteurella in vitro. *Past. haemolytica* was grown from several sites in these lambs. A search for clostridial toxin was unsuccessful."

The Reply

Mr. A. J. Stevens, in reply, suggested that though the Scots present were reticent about the occurrence of jaagsiekte in Scotland they all appeared to have seen it, though some even made an attempt in the discussion to disguise it as parasitic pneumonia!

If, as Dr. Watt had suggested, the Greyface sheep showing the disease had been bred from draft Blackface ewes and had contracted jaagsiekte from them then we might expect to find a high incidence in the Blackface flocks themselves, and to his knowledge this did not occur. However, Greyface sheep were not always bred from draft ewes. The actual incidence needed further investigation.

The diagnosis of jaagsiekte, like so many other diseases, depended on the consideration of many factors, not just one. Pasteurella pneumonia was usually an acute flock condition and the organism was readily cultured. The lesions were often localised to the apical and cardiac lobes. Jaagsiekte was more frequently a very chronic pneumonia affecting only a few sheep at a time. The area of lung involved was often extensive and there was gross enlargement and much fluid present. Cultures were sterile except when abscesses had formed. The distribution, extent and histological appearance of parasitic lesions was different from jaagsiekte.

Stress factors were most important in relation to enzootic Pasteurella pneumonia, but he knew of no direct scientific experiments to study the exact relationships involved.

The Veterinary Clinician's Approach to Breeding Problems in Mares

BY
F. T. DAY
Newmarket

THE first essential for any veterinarian working with breeding mares is to be able to carry out pregnancy diagnosis at all stages of pregnancy.

Clinical examinations of genital organs, either in the breeding season or out of it, are always made with the object of finding out if there is any abnormality of the breeding organs and to determine what treatment, if any, is necessary and as pregnancy is one state of the breeding organs it is essential that it should be recognised at any stage.

Clinical Examination of Genital Organs

Examination of the ovaries and uterus per rectum; examination of the vulva, vestibule, vagina and cervix with a speculum and inspection lamp; digital examination of the cervix and the lining of the uterus within reach of the finger inserted through the cervix—these are the limitations of our routine clinical examinations of mares' genital organs.

It is worth while mentioning here that it is impossible to palpate the fallopian tubes, but this is of little consequence as, in the mare, they are singularly free from trouble.

Rectal examination only is used for pregnancy diagnosis.

In carrying out these examinations, there are great differences in the ease with which detailed examination per rectum can be made. If mares relax the rectum, then it can be very easy, but all degrees of difficulties are met with and patience is usually rewarded. If mares do not relax readily, the most helpful thing one can do is to insert the speculum in the vagina and then resume examination per rectum and this is invariably successful.

Pregnancy Diagnosis

Pregnancy can usually be detected by rectal examination at 30 days, but to avoid check examinations we only carry out routine pregnancy diagnosis at 40 days.

When examinations are made at this stage there is quite a variation in the size of the foetal sac. This is partly due to the 40 days being taken from the date of service, and not from ovulation, which can give up to a 6 days difference, bringing it back to the 35 days size.

Apart from this, however, there must be occasional delay in the early developing foetus as some exceptionally small foetal sacs are found where the longevity of stallion sperms would not alone account for such a disparity.

If the foetal sac is too small, a check examination should be made a week later to ensure that it is still growing; some do, and pregnancy continues normally, but in most cases the foal is carried overtime. Many fail to go on growing and remain *in situ* at the same size and are only extruded when the mare comes in season.

In some thousands of examinations I can recall about 6 mares in which I could not find a foetal sac at 40 days, and which I examined later, because they had not come in-season, and found them to be in foal. The size of the foetal sac in these cases was about 20 days undersize from the date of service, and although one naturally felt that there had been another later service, I was assured on each occasion that this was not possible, and so one must accept them as strange extremes in delayed early foetal development. Where time permits, and if mares diagnosed as empty at or around the fortieth day of pregnancy fail to come in oestrus again, a final check should be made about a fortnight after the original diagnosis.

Very occasionally one finds a small foetus, when examining mares in oestrus, lying on the floor of the vagina.

It is essential to remember that there will be foetal death at all stages of pregnancy, and that the earlier one examines mares for pregnancy the greater will be the number of mares which subsequently fail to have a foal, although known to be in-foal at the time of examination, and without those in charge ever seeing any sign of abortion.

It is hard to produce absolute figures, but in one Private Stud where accurate records have been kept for just over 200 mares, during a period of some 10 years, it looks as though the disparity between mares being diagnosed as in-foal at or around the fortieth day and those subsequently proving to be in-foal is about 8–9%; including noticed early abortions as opposed to nothing being seen, the figure would be 10–11%.

Human nature being what it is, owners are very apt to think that this difference is mainly attributable to our inefficiency in diagnosis and for this reason a few prefer not to have their mares examined.

It is essential to emphasise that early pregnancy diagnosis is not a guarantee that pregnancy will continue normally; it is employed only to find out the mares which are not in-foal during the breeding season so that further efforts can be made to get them in-foal without loss of time.

This has been accepted at the major sales of brood mares, where certificates of pregnancy are only accepted for mares examined within a month of the sale, and as these sales are in the winter and autumn we no longer have the annoying business of owners lodging 6 weeks pregnancy diagnosis certificates as a recommendation of mares being sold in the late stages of pregnancy.

In the earliest stages of pregnancy the foetal sac usually develops in the uterine horn, but very occasionally in the body where it is much more difficult to palpate.

I should also like to mention here that up to about sixty days, it is possible to feel twin pregnancies, but after this time the individual foetal sacs grow so that they merge into one and twins can no longer be diagnosed.

In diagnosing pregnancy only distension of the uterus by the foetal sac is felt until about 100 days, and then the foetus itself is first felt, rather in the way that one would touch a floating apple, bobbing against the hand. It is only after the seventh month that one immediately contacts part of the foetus.

Even as early as the 21st day onwards of pregnancy, the turgidity of the uterus, together with the tacky appearance of the mucin on the cervix are very good guides to pregnancy, and the earliest time that a foetal sac can ever be felt is about 25–27 days.

Differential Diagnosis

There are two conditions of the uterus when examined per rectum, which could be confused with pregnancy.

Firstly, at about 40 to 60 days, the uterus may have a sac-like distension, which could simulate pregnancy, but it is a little more doughy to the touch, and the clinical picture of the vagina and cervix show an infected and inflammed appearance; this results from old damage to the cervix, and the early accumulation of uterine secretions. All sizes of distension can occur, but the earlier one is the most easily confused with pregnancy.

There is also a temporary condition of old mares whose ovarian behaviour is abnormal in which the whole uterus becomes distended with fluid and in which the cervix is quite normal, but again there is the inflammed appearance of the vagina and cervix, this condition is not unlike pyometra in cattle.

Although in normal pregnancy the vagina and cervix are pale and the mucin is dry and sticky, occasionally a rather inflammed appearance of the cervix and vagina is found in pregnancy at all stages and occasionally even a vaginal discharge; so great care should be taken in differential diagnosis.

Mares which Fail to Come in Oestrus

This includes mares which have been tried during the season for some time without showing signs of oestrus and those which have not shown signs of oestrus by the ninth day after foaling. If the ovaries are normal in size with palpable follicles of approximately 2 cm. diameter or more, and the mucous membrane of the cervix and vagina is a uniform pink and the mucin moist, treatment is seldom necessary unless they are mares which will not show.

Bearing this in mind it is sometimes advisable to make frequent examinations to ensure that the mare is not having unobserved heat periods (silent heat). This occurs very frequently at the first oestrus after foaling.

At this point it is worth emphasising how early mares can be in oestrus after foaling. All too frequently we find ovulation has already occurred on the ninth and sometimes even the eighth day from foaling. This is commonest in mares with a foal at foot, and a few mares have to be examined every year to detect oestrus. Although they won't show to the horse, if there are normal physiological signs of oestrus they are seldom any trouble to get covered.

If mares have follicles in the ovaries, and the vagina and cervix are dry and give the appearance of a pregnant mare on the cervix, they should be treated without loss of time.

By far the best form of treatment is gravitation of warm water into the uterus. About a pint of water at body temperature with a tablet of Chinosol in it is our usual procedure. Oestrus should follow within three to five days and is usually of normal duration and accompanied by spontaneous ovulation. It is surprisingly effective and there are comparatively few failures.

One unfortunate happening does occasionally occur, a mare develops a vaginal discharge and fails to come in oestrus—the discharge continuing for weeks or months until oestrus does occur and then recovery is spontaneous.

I am at a complete loss to understand this and treatment of discharge which has occurred in this way, has so far been useless. Fortunately it is a comparatively rare sequel.

I wondered if manual manipulation of the cervix and the insertion of pessaries into the uterus would have the same effect as gravitation of water into the uterus. It does give occasional results but nothing like as good as that already mentioned.

When there is a large follicle in one ovary and a dry cervix and vagina, stilboestrol (15 mgs) given subcutaneously occasionally gives a 24–48 hour response of oestrus with spontaneous ovulation, but it is too unreliable to be recommended.

With a similar clinical picture, particularly if there are two very big follicles in the ovaries, ovulation of one or both can be induced by luteinising hormone (intra-venously)—oestrus does not occur with the ovulation, but does ensue at the expected 16–21 day period after ovulation.

If ovaries are very small without any palpable follicles—any treatment is better delayed as no worth while response occurs until the mare has produced follicles up to about 2 cm. size.

As barren and maiden mares tend to have long oestrous periods early in the season, and these gradually become shorter as the season advances, particularly when the first bite of grass comes along, we usually delay treatment to induce oestrus in these mares until the end of April, although we are guided a little by the mare's bodily condition and her coat.

Coat-shedding is often an indication of improved ovarian behaviour. I once saw a barren mare with the longest coat I had ever seen, arrive at a stud for mating, but she developed loss of co-ordinated movement and had to be destroyed. She had a tumour of the pituitary and I am sure the exceptional coat, and the tiny anoestrus ovaries, resulted from this condition.

Oestrus

There are great differences in outward display of signs of oestrus in mares, and also great differences in length of oestrus. The long oestrous periods are usually in maiden and barren mares in the early part of the season, but occasionally also in foaling mares.

Detecting oestrus means a lot of work for the Stud Groom, trying and observing mares at all times, and he most of all appreciates the help we can give by examining all doubtful cases.

Oestrus frequently occurs without ovulation and vice versa. It is very rare for oestrus to continue for more than 24 to 48 hours after ovulation occurs, except when there are twin ovulations with a separation of some days between them.

When ovulation occurs it is usual for the interval between oestrous periods to be about 17 days, and the range from 14–20 days. If ovulation does not occur, the interval is usually 7–10 days between heat periods.

Time of Mating

For practical purposes a mare needs to be covered within 3 days of ovulation to have a reasonable chance of becoming pregnant. Fortunately many mares get in-foal when the interval is greater, but there is an appreciable falling off in chance, up to a known extreme of 7 days.

Mating after ovulation is complete is never successful.

Trying to Determine Time of Ovulation

Examination of mares' ovaries tells you the size of follicles. Size of follicle should be related to total ovarian size and to position in the ovary, as centrally placed follicles start nearer to the ovulation fossa than those at the poles of the ovary. A 2 cm. follicle on a very small ovary is comparable to one of 3 cm. or more on a large ovary.

One examination does not indicate the rate of growth of the follicle. An assessment has to be made on tenseness or softness of the ovarian follicle, the time of year (they grow faster in May than in March); the size of ovary and the degree of relaxation of the cervix are further guides. With experience one is able on one examination to be right in more than 50 % of cases in deciding whether ovulation will occur within 3 days.

This leaves a lot to be desired and so one has gradually got everyone concerned educated into the habit of making check examinations two or three times weekly.

When several mares are in oestrus to the same stallion it is important to try and give them all their best chances and then luteinising hormone (intravenously) is most useful in ensuring ovulation in some of the mares. If mares have a follicle of approximately 3 cm. diameter or more then luteinising hormone will induce ovulation.

It is not advisable to give luteinising hormone intravenously without checking the size of the ovarian follicles. I have known of cases where it was given early in oestrus when stallions were busy, without examination of ovaries, and in the dose mentioned it had no worthwhile affect.

In giving luteinising hormone, we usually instruct the stud to let us know when the mare has had a good service by the stallion and then give it as soon as possible afterwards. Occasionally with sub fertile horses we inject the day before covering to minimise the time between service and ovulation.

Injection of 1,500 I.U. luteinising hormone (i/v) induces ovulation in about 40 hours, and if the material is of proved worth it is over 80% effective.

It is worth mentioning here that 1,500 I.U. is the minimal effective dose, and when it fails, it probably means it is too small a dosage. In mares with grape-like ovaries, we know the dose will probably be too small and give between 3,000 and 5,000 I.U. according to our assessment of the mare.

Regression of Follicles

Some mares can be very tiresome by going out of oestrus without ovulation, and this occurs at all stages of maturation of the follicle. Many is the time I have wished I had given luteinising hormone (i/v) instead of having to wait for another heat period. Once a mare has done this, I always give luteinising hormone (i/v) next time she is in oestrus with a decent follicle. It is more common with the barren mare with rather large ovaries, ovaries which always seem to have too many small follicles in them and are best described as like a small bunch of grapes.

Ovulations and Twin Ovulations

Ovulation is readily detected by the pit in the ovary. When feeling a recent ovulation it is usual for the mare to lift the hind leg up on the side of the ovary concerned, as if it were slightly painful. After about 8 hours, there is friable blood clot in what was the pit and this is easily detected; this becomes firmer in 24 hours but pits on pressure, but at 48 hours is plummy in consistency and not always detectable with certainty. The corpus luteum of the mare cannot be detected after 48 hours from ovulation.

Sometimes follicles rupture on slight pressure and ovulation is induced a little early. In a few cases of rather large follicles I have purposely exerted great pressure with one hand in the rectum and the other in the vagina and have induced ovulation, and in several cases have had pregnancies to the induced ovulation. It is just of interest to know that the ovum can stand up to such pressure and be none the worse for it.

Twin ovulations are very tiresome and occur all too frequently; usually there is one follicle in each ovary, but occasionally two follicles in one ovary. As a rule they tend to occur together but I have known them at every interval up to 10 days apart, although the majority occur 0–3 days apart. If we find them on examination we try to allow one to ovulate and then cover in time for the other. It is most difficult to do the right thing. They so often ovulate in the same 24 hours. One can puncture one follicle with an ovarian needle, but one hesitates to use this as a routine, as it is not always easy with a fractious mare.

If one follicle does ovulate and gives time for service for the other then I usually give luteinising hormone (i/v) to ensure ovulation. It is very tiresome when you think you have done the right thing and the second ovulation does not occur!

It is impossible to guarantee to prevent twins in the mare by checking ovarian behaviour. A lot can be avoided, but I am sure that some follicles which on palpation give the impression of being one, must be two developing so closely that they feel as one.

In a mare which threatened to have twin ovulations, I once ruptured one follicle by pressure per rectum—through the ovulation fossa of course, and had the mare covered two hours later and the second follicle ovulated spontaneously. She produced twins—which means that by this method of emptying a follicle the egg does not necessarily come out as soon as with natural ovulation.

One interesting record is of a mare which had twin ovulations three days apart and which had been covered before both ovulations. As an experiment I washed out the uterus with a quart of warm water 6 days after the first ovulation and she became pregnant on the other one. This is of interest as the other fertilised egg must have come into the uterus two days after gravitating it full of fluid, and yet implantation occurred and a normal pregnancy ensued.

Before mentioning this case, I should perhaps have stated that the ovum is in the fallopian tube for 5 days after ovulation, but is always in the uterus by the sixth day.

When we know that mares have had twin ovulations and have been covered to give both a chance of being fertilised we wash out the uterus 6 days after ovulation. Mares treated this way invariably come back into oestrus in about 10 days, the normal period of the non-pregnant luteal phase. This is interesting as it is longer than the period of the mares which we usually treat to bring into oestrus and indicates that few of the latter are in a luteal phase. Also, although we have washed out a lot of would-be twins, I have never known one of these mares show a vaginal discharge.

Mares having a Vaginal Discharge

This may vary from a few smears on the buttocks, and a slight soiling of the tail, to a profuse discharge. It should not be confused with the deposit of salts from urine which is occasionally seen down the inside of the thighs.

The chief causes are as listed below:—

(1) Mares which have not contracted up after foaling and have a large uterus with metritis. These are best treated with antibiotics locally in the uterus and parentally.

(2) Mares with a previously damaged cervix—with scar tissue and adhesions and a subsequent chronic metritis.

If the cervix is damaged, the mare will be permanently sterile. I know of no worthwhile treatment.

(3) A condition simulating pyometra in cattle. Usually associated with " bunch of grape " ovaries and irregular cycles. Some cases have responded to implants of Stilboestrol—1 gram subcutaneously for 2–2½ months. The ovaries become small and anoestrus and the uterus returns to normal. Some mares have bred successfully, others have had a return of the condition after removal of the implant.

Included with this group are mares having the large grape like ovaries, usually with an irregular cycle, in which ovulation is all too rare, but whose uterus is not unduly abnormal although there are alternate periods of the mare appearing to be normal on examination of the vagina and cervix, and other periods when they show a variable amount of vaginal discharge. It should be mentioned that during the period of the implant, mares show typically male behaviour.

(4) The largest group are mares which are sucking in air through the vulva. This is most commonly met with in older mares but occasionally in maiden mares sometimes when they are still racing.

The symptoms vary with the degree but it is the most important single clinical entity we have to diagnose and correct. Grooms may hear mares " rattle " in the paddock. Examination per rectum may reveal the uterus or the vagina full of air. When stallions cover such mares they do not appear to relish their work and have difficulty in ejaculating. They also behave in this way if asked to cover a mare which has just been examined with a vaginal speculum. The position of the vulva in relation to the floor of the ischium is an important factor, as are also the degree of falling in of perineal region, and thinness of lips of the vulva.

Usually the speculum shows a degree of overballooning of the vagina, possibly with dilation of the cervix. There is a variable amount of discharge from a few frothy bubbles of mucin to a more copious catarrhal exudate.

Those that are severely affected are easily diagnosed—but there are many borderline cases, mares which might breed if not treated—but would have a much greater chance if they were.

Treatment consists of suturing the upper commissure of the vulva to prevent pressure of the atmosphere exerting itself against the vaginal walls. This is very easy and straightforward in most mares, but in a few with a very fallen in perineal region in which the vulva is nearly horizontal, it is difficult to stitch enough and still allow room for the stallion.

It is not necessary to stitch in any great depth—just sufficient for it to be safe to cover without the stallion tearing it. Once mares have been effectively stitched the symptoms previously seen make a surprisingly quick spontaneous recovery.

After stitching we like stud grooms to cut the stitched part with scissors when the mares are foaling to prevent it bursting and causing splitting and ragged edges. They are then stitched again the morning after foaling and it is usually possible to have them covered on their ninth day heat period, if a deep strong protective suture is inserted at the lower end of the stitching.

(5) Mares which have been normal and suddenly have a slight vaginal discharge just before and during oestrus. The discharge does not appear to be related

to any trouble with the vulva and it can only be assumed it is a primary metritis.

If the heat period can be missed, treatment with antibiotics locally and parentally usually cleans them up. Many mares respond to antibiotics in pessary form put in the day before covering and then again the day after ovulation with normal pregnancy ensuing.

A word about the bacteriological side—a normal mare's vagina, cervix and uterus are sterile, and the clinician is well able to decide when they are normal. If mares have a vaginal discharge or an inflammed vagina and cervix then there is a reason for it. Bacteriological cultures invariably show a pure or contaminated growth of haemolytic streptococci and seldom any profuse growth of the contaminants. It is rare for us to take cultures any longer, the information they give does not help us materially. The mares which suck air demonstrate this; (bacteriologically you could write a book about them) stitch them up and the bacteria disappear.

Fortunately we do not have any venereal disease amongst horses which has a direct bearing on fertility. There is, however, one condition which should be mentioned. This is a typical pox-like condition which can occur in mares and stallions, but which is confined to the external parts of the genital organs, viz. the lips of the vulva in the mare and the external parts of the penis in the horse. It starts with vesicles which rupture, become ulcers and heal. The duration of the condition from start to healing is under 14 days. It has no bearing on fertility. Its nuisance value is that if a horse gets " spots " you must stop covering, or he gets more spots by reinfection; and in the horse there is a risk of secondary infection at the ulcer stage.

If mares have spots in one heat period, they make a spontaneous recovery and can be covered in the next heat period.

The condition is frequently seen in mares and stud grooms are always checking for it, so that stallions only rarely get it.

(6) Mares with a recto-vaginal fistula. This can be a fistula of any size between vagina and rectum to a common cloacal opening where the anal ring is torn and several inches of vagina and rectum are as one common opening. They are caused by the foal's nose or foot being forced upwards into the rectum at foaling, and it is an accident which is almost entirely confined to mares having their first foal.

I know of one such mare only which bred for three years without surgical treatment, though usually it is a cause of permanent sterility.

Both types can be repaired surgically under epidural anaesthesia. Attempts to operate shortly after foaling have not been successful. It is advisable to leave them until the mares are weaned, since careful preparation by controlling amount and consistency of faecal material to be passed after the operation, has been found to be of such importance in ensuring successful healing.

Here I must give credit to my partner who does our major surgical work. He has operated on a number of these cases and two of them I never anticipated could be restored to breeding efficiency, but those that have been repaired have all to date bred again, and, to my surprise, without any tearing of the platform created between rectum and vagina even in the two extremely bad ones.

Abnormal Ovaries

It is difficult at times to decide whether ovaries are abnormal, or whether they are merely an expression of abnormal pituitary stimulation. In the majority of cases I think the latter, except for those to be specifically mentioned.

Unless one is confident that an ovary is abnormal it is better to give it the benefit of the doubt. I have had many pleasant surprises with large doubtful ovaries, when I have patiently waited for a follicle of reasonable size to develop, and have had the mare covered and given a large dose of luteinising hormone (i/v) and have checked an ovulation. Confirming pregnancy in such mares about 6 weeks later is a very pleasurable experience.

As already mentioned, ovaries vary immensely according to time of cycle, and there are basically large and small ovaries, although clinically one distinguishes a range of normals. I have mentioned one abnormal type—the grape-like ovary; with this condition it is usual for both ovaries to be of the same type although they may differ appreciably in size. If these are both very large then experience suggests they will not get in-foal during that season. If time permits it is worthwhile giving a Stilboestrol implant which brings the ovaries down to anoestrus size. This is best timed so that the implant is removed at the beginning of the breeding season and several such mares have been got in-foal at their first subsequent oestrus. Others revert back to the old condition.

There are several other types:—

(1) Very small ovaries in maiden mares of haricot-bean size. Most of these ultimately get bigger and mares breed alright. This may occur within a season or may be delayed for a year.

Two cases are known which never bred and the ovaries remained small.

(2) Very small ovaries, of broad-bean size or a little bigger, are not uncommon in mares with first foal at foot. May be temporary only for a few weeks or may result in barrenness for the year. Never permanent.

(3) One very large abnormal ovary, which feels hard and does not produce follicles but where the other ovary functions normally. May or may not result in sterility. Tend to get progressively worse and usually do. Removal of affected ovary allows normal breeding on the other ovary.

(4) One very large ovary partly follicular and where the other is very small and always devoid of any follicle. There is usually a tumour of the affected ovary and in my experience it has only been unilateral. Removal of ovary restores breeding efficiency and the inactive ovary becomes fully functional. These mares usually start by showing continual oestrus and then show typically male behaviour, even mounting " in-oestrus " mares.

Removal of Ovaries

In all these large ovary cases, when the ovary has been too large for removal by operation *via* the vagina, it has been found that a 1 gram Stilboestrol implant will reduce the size of the affected ovary to enable this to be done.

Progesterone Implant

While dealing with implants I should like to mention a series of mares which had previous records of abortion late in pregnancy. For want of something to do, I have implanted about a dozen such mares with 3 × 50 or 3 × 100 mgs progesterone, between the 130th and 150th day of pregnancy. To date all have carried full time and the implant has been removed about a fortnight before expected parturition. I mention this primarily to show that no ill effects resulted from the treatment, but with so few it is impossible to say if it did any good.

The Stallion

There is a great basic difference in the levels of potential fertility in stallions. This is apparent when working with the mares, knowing their opportunities. It is a pleasure to work with mares with a first class foal getter. Equally it is soul destroying when the stallion is not playing his part.

If stallions are not really good foal getters there is nothing one can do, assuming that management and feeding are good, except minimise the interval between covering and ovulation by checking the mares.

Checking Covering

Many stallions will occasionally give the appearance of covering without ejaculating. The simplest way to ensure that ejaculation has taken place is to hold your hand under the base of the penis. When they do not cover, a few weak urethral waves may be felt, but when ejaculation takes place it feels like the contents of a 10 c.c. syringe going along the urethra. In a stallion of good fertility it is usual to feel about 5 of these waves; in the lower fertility group it is sometimes only about 1½.

Stallions when covering should ejaculate straight into the uterus and in most cases there is very little semen left in the vagina. Insemination as carried out to transfer semen from the vagina to the uterus is seldom necessary, but it is recommended with wriggling mares or if a stallion is apt to come off his mare with the penis still erect, as this pulls semen back into the vagina.

Semen Examinations

Samples collected from a mare are a good guide to potential fertility if they are very good samples, but they are very variable and a poor sample is not a very good guide. A series of poor samples without being able to get a good one, certainly is.

Collection with Artificial Vagina

Many horses will use an artificial vagina very satisfactorily and samples collected in such a way give a very good idea of their fertility. Inseminations from an artificial vagina are the ideal from the technical point of view, but are not practical on any scale. They are only used in cases where it would not be advisable for the stallion to mount the mare.

Discussion

From the clinician's point of view, to get good fertility results, he needs a mare with a normal genital tract, to have that mare in oestrus, covered, and with ovulation occuring within 3 days of covering. When all these happenings occur, there is a 70% chance of pregnancy irrespective of the mare's previous history.

He must have a fertile stallion.

Pregnancy diagnosis must be used as a routine as early as possible.

He (the clinician) must adopt the attitude that pregnancy is the best cure for sterility and every chance offered of a successful covering must be taken.

While using the stallion's services to give all mares a good chance of getting in-foal, any undue saving of stallion's services must be followed by a falling off in fertility. In my experimental work I was forcibly struck by the difficulty in fertilising mares' eggs and feel sure that the more semen there is in a mare's uterus the better her chance of getting in-foal. This is why a few particularly good foal getters are outstanding amongst stallions, and also why, if all else fails in a mare which appears to be normal, I should always try turning her out with a stallion to get her in-foal before giving up hope.

Where do Clinicians Need Most Help?

We should like to be able to have some means of influencing follicle growth in a mare's ovaries at any stage from anoestrus onwards.

We should like to be sure that luteinising hormone, when ordered, would necessarily be effective when given to mares. At present we have to check each batch. Recently we have been fortunate, but in the past we have had material which was quite useless, although the drug houses concerned assured us it was active when assayed on rats. Our only reply was that we were not interested in rats!

We should like to be able to improve libido in slow stallions and to influence ability to ejaculate in those which mount several times before managing it.

Are testosterone implants the answer? If so—is there any likelihood of an adverse affect on sperm production either for short or long term policy?

Is there any likelihood of finding a means of increasing the potential fertility of horses of lowered fertility level? Personal experience suggests that feeding additives in all their various forms are useless.

Postscript

I forgot to mention the advisability of examining every maiden mare prior to the breeding season; firstly, to ensure there is a complete breeding apparatus. I have found three mares with incomplete genitalia, one without uterus and cervix, one without a uterus, and one without a cervix.

It is not rare to find varying degrees of bands of tissue across the vagina, these can usually be severed with scissors, but might cause deflection of the stallion's penis at covering and tearing of the vagina if not attended to.

It is not uncommon for mares to have haemorrhage from the uterine artery into the broad ligament and in close proximity to parts of the uterus.

Every year we see several of these cases, some have shown clinical indications immediately after foaling, others not.

If found when examining mares at the ninth day after foaling, it is advisable to delay mating until the next heat period—or the stallion may cause further damage.

This can occasionally cause temporary sterility or even permanent sterility. I have known one or two mares which had a partly organised gross degree of haemorrhage which mechanically pulled the uterus down so far that it resulted in permanent sterility.

The Opener

Mr. C. S. Haselden (Aylesbury), who opened the discussion, said that he had known Mr. Day for very many years and there was no doubt he was one of the greatest experts in the world on the subject. That should be kept in mind, as what seemed easy to him was considerably more difficult for lesser mortals. Particularly did that apply to the very early diagnosis of pregnancy. Although he did not doubt Mr. Day's ability to detect pregnancy usually at 30 days, he himself would not attempt it as he could not see any practical application. Mares' uteri varied considerably, and it was obviously much easier to palpate the foetal sac in a mare carrying her first foal than it was in the case of a mare that had had ten or a dozen foals and had a dropped and greatly thicker uterus. He found it simpler also in mares whose ovaries he had examined three or four times previously in the same season and whose non-gravid uterus he knew.

In Mr. Haselden's opinion, there was considerable risk in making a definite negative diagnosis prematurely. He had a horror of washing out a perfectly good early foetus and could imagine nothing more embarrassing to the veterinarian or more annoying to the owner. Examining a mare at 6 weeks was comparable to examining a cow at the same stage. It was largely a question of practice and some people got the knack of it more quickly than did others. He would strongly advise any veterinary surgeons who examined only six or a dozen mares a year not to attempt such examination under 50 days, and preferably longer. A small percentage of his clients still preferred the biological test, either of blood or urine. Rather erratic results had been obtained with both methods, and before drastic steps were taken he advised that the diagnosis should be confirmed, in all cases, by a rectal examination.

Mr. Haselden was glad that Mr. Day had raised the matter of undetected early abortion. He had not realised that the proportion was as high as Mr. Day stated, but it commonly happened and nothing was thereafter visible. That was proved by the rare case in which a mare was actually seen to abort, or when a small foetus was found in a loose-box. Careful examination of the mare revealed no discharge on the tail, vulva or thighs, and in this connexion it had to be remembered that a 50-day foetus was only about the size of a mouse.

He did not think it either practical or necessary to be continually examining every mare in oestrus to see if she was ovulating, and approximately when ovulation would take place. On the other hand, they could be of great assistance to the stud groom when several mares were on at the same time to one horse, or if the stallion was not very virile—and, obviously, when a mare was not having normal oestral cycles. He mentioned that because there was an increasing tendency, especially amongst the younger stud managers, to want every mare examined two or three times when in oestrus.

In one stud where Mr. Haselden worked, one of the stallions was very old. Last season he had covered 32 mares, 25 of which had been tested to be in foal out of a total of 56 services. He had not examined anything like all those mares prior to service, but in that particular case there was an extremely able, co-operative and conscientious stud groom and that was more than half the battle. Nor did he agree with the practice adopted by some owners who sent a mare to the stud—often a considerable distance away—with a note to say she would be just right to be covered the following day and that they would pick her up again in a day or so. All too frequently one found the mare had gone off and ovulation had occurred. In one such case where the mare had been covered 3 weeks before he had persuaded the owner to leave her. When, after a further 3 weeks, she had not come on he had found her to be in foal. What did Mr. Day consider to be the frequency of mares already in foal to a previous service returning again into oestrus or partial oestrus later?

Twin ovulations were a great headache, and he would rather miss that oestrus altogether, if possible. If one follicle was allowed to rupture and the mare covered and given luteinising hormone two days later when it was thought the second was just ripe, what guarantee was there that the first egg might not also be fertilised? He was glad that in his experience twin ovulation occurred much more frequently early in the season than later.

Mr. Haselden agreed that the aspiration of air was the commonest cause of infertility, and in that connection the conformation of the animal had a very marked bearing. When asked his views about a mare, one of the first things he looked at was the shape of the vulva, while keeping in mind the animal's physical state at the time. It was surprising how rapidly the condition responded to stitching. Bacterial infection cleared up, the uterus and the vagina resumed their normal size and position, and, in the case of the vagina and cervix, their normal colour. That was true even in the extreme case where one found a large pool of urine on the floor of the vagina, with a consequent acute cervicitis. In what he would describe as the moderate case seen for the first time in oestrus he had adopted the practice of waiting until there was a really good follicle, then inseminating the mare, giving 1,500 i.u. of luteinising hormone intravenously and stitching forthwith. He had had so many successful results in this way where mares had previously turned that he could not think it a coincidence, and wondered whether Mr. Day adopted the same routine.

Continuing, Mr. Haselden told his audience that for many years he had attended a large Arab stud. Despite the unbelievably small vulva of the Arab mare he had never known one to be torn at foaling, or to aspirate air, even in extreme old age. The same applied almost equally to the Anglo-Arab. This he could only attribute to their very rounded quarters and the better formation of their external genitalia. On the other hand, aspiration of air was as common in the part-bred hunter mare as in the Thoroughbred.

What did Mr. Day think to be the maximum size ovary removable with safety per vagina? The largest he himself had so removed had been the size of a smallish coconut. Further, had Mr. Day had any success with a stilboestrol implant where a tumour was suspected and had he ever experienced post-operative haemorrhage? The latter had not occurred in any of his own cases. He took plenty of time in crushing the ovary off, but he was quite sure that one day in the case of a very vascular ovary it would happen.

One surgical condition which Mr. Day had not mentioned in his paper was that of complete prolapse of the uterus and vagina. Over a period of years, that condition seemed more common in Arabs than in Thoroughbreds, possibly because they were usually very fat, with consequent lack of tone in the broad ligament. The cases usually suffered very severely from shock, and on more than one occasion he had known a mare to die before any attempt had been made to reduce the condition. He treated the condition by first giving glucose intravenously followed by pituitrin and chloral intravenously. He usually found that to be a narcotic sufficient to prevent undue straining. If it was

not, he preferred to give a small dose of chloroform standing rather than an epidural, in case one misjudged the dose and the varying reactions, as there was nothing worse than a mare staggering about with only partial control of her hind legs. It was of the utmost importance to reduce the condition completely. If the end of one horn was left slightly invaginated the mare would commence to strain and the whole thing would recur. He had found recovery to be rapid and in each case the mare had bred again.

How right Mr. Day had been when he said that the virile and fertile stallion was a joy to work with. It was all very well to say that the easiest way to tell if a stallion had ejaculated was to hold one's hand under the base of the penis but some stallions would not allow that. He had one stallion in mind that would drop his head and his tail would go like a pump handle. Nevertheless, he had not ejaculated, although any stud groom could be excused for thinking he had. After two or three minutes the stallion would draw again and perhaps be lucky. Mr. Haselden thought that that happened with many stallions much more frequently than was imagined.

With high-class horses fetching such astronomical prices buyers were beginning to insist on a test fertility prior to purchase, but in the case of a horse just out of training that could be very misleading. He knew of one horse that raced at 2, 3, 4 and 5 years of age. When examined in the October he was found to have testicles of yearling size and his semen samples were unsatisfactory. Quite rightly, he was turned down. Mr. Haselden had insisted that this horse should not have any mares in the next season apart from a couple for fertility tests, neither of which were put in foal. The semen improved greatly, and they took a chance with him. It was believed that in the present, his third, season the horse had got in foal 40 mares out of 45.

Mr. Haselden said he had read with interest in one of Mr. Day's concluding paragraphs: "If all else fails in a mare which appears to be normal I should always try turning her out with the stallion to get her in foal before giving up hope." To that Mr. Haselden would add, "and she probably will be in foal." Much progress had been made in the last 20 years but there was still a long road to travel before they caught up with Nature.

The General Discussion

Dr. G. H. Arthur (Streatley). "Mr. Day has made considerable contributions to the study of horse breeding and I have found his current paper as interesting as his previous ones. During recent years I have had to familiarise myself with equine breeding problems and to this end, as a beginner, and believing *post-mortem* inspection to be preferable to clinical examination, I examined during 1949-51 some 792 reproductive tracts of mares slaughtered in London. This was possible through the kind help of Mr. H. E. Bywater. The main features which arose from this study and which are now in the press were as follows:—

"1. There is, within normality, tremendous fluctuation in the size of equine ovaries, depending mainly on the number and size of contained follicles.

"2. Apart from the identification of sizeable follicles and very young corpora lutea, one can only guess at the ovarian content, even on the *post-mortem* table. To be certain, it is necessary to make a series of sagittal sections—not just one down the middle of the ovary.

"3. It has not been possible on *post-mortem* examination to recognise cystic ovaries. The largest follicle seen was one of 10 cm. in an ovary of an apparently normal pregnancy. It is believed that the cysts which are diagnosed clinically are simply follicles in various stages of development. Also it would seem that the belief that cystic ovaries cause nymphomania in mares needs revision. In 8 cases of troublesome mares subjected to ovariectomy at the Royal Veterinary College in recent years the ovaries appeared normal. Some were ovaries of dioestrus, others of anoestrus and one of near oestrus. It is, of course, possible that female hormone in normal amount may condition the central nervous system to environmental stimuli and lead to exaggerated response, but the not inconsiderable percentage of failures recorded following ovariectomy reminds us that organs other than gonads are concerned in behaviour.

"4. Twin ovulation is very common in the mare—a view I first put forward at a discussion of a paper by Mr. Day before the Society of Animal Breeding in 1952. Its extent parallels the degree of ovarian activity and its highest incidence is from June to September but it has often been seen in winter specimens and breeding early in the season will not avoid it. Our monthly average percentage of double ovulations for the 3 years studied varied from 5 to 37.5 and the highest for any single month was 50 per cent. in September 1951; this included 3 triplet ovulations. In Mr. Day's earlier papers there was no mention of multiple ovulation except in one Percheron mare which had been given gonadotrophic hormone. He now says that twin ovulation occurs all too frequently. Can he give an approximate figure from clinical examination? Having regard to the length of heat and the inconvenience of repeated examinations it must be very difficult to diagnose twin ovulation clinically. I believe that the incidence is much higher than clinical examination would reveal. The chief importance of double ovulation is that there appears to be a much higher degree of embryonic resorption following twins rather than singles, as first pointed out by Hancock (1948). In addition therefore to the obvious abortions and births of non-viable foals associated with later twin gestation, this phenomenon was the cause of 'physiological' infertility as well as for some of the false positive results of early pregnancy diagnosis tests.

"The means available for preventing twin ovulation were unsatisfactory. If one of two follicles was purposely ruptured it was feasible that another would grow quickly and replace it and in any case, triplet ovulation was also possible. Incidentally, one wondered whether luteinising hormone might increase the number of twin ovulations.

"5. In respect of ovarian activity our records show little difference of function between right and left; actually 52.2 per cent. of ovulations were from the left ovary. Another rather unexpected finding was the amount of cyclical activity which occurred in winter; it varied from 16 to 63 per cent. from December to April. True anoestrus in winter was not as common as had been anticipated. Clinically it was not easy to distinguish anoestrus from dioestrus and they were probably confused. In the treatment of lack of heat stilboestrol can be dangerous in that it may cause nymphomania but the intra-uterine instillation of 200 c.c. of boiled water seemed harmless and apparently useful.

"6. As regards abnormalities of the genital tract in relation to infertility we have been impressed by their rarity—at least in abattoir specimens, although we did not examine the vulva or vestibule. This confirms a previously expressed view of Mr. Day that infertility in mares is mainly functional. Parovarian cysts, particularly of the epoophoron are very common and vary in size up to 7.3 cm. but one cannot see how they can interfere with fertility; but on rectal exploration they could cause confusion in feeling like a part of the ovary and lead to a diagnosis of 'cystic ovary.' In our 792 specimens we saw only 2 cases of hydrosalpinx and none of ovaro-bursal adhesions. There were 8 instances of macroscopic uterine abnormality comprising 1 of pyometra, 1 of generalised cystic hyperplasia of the endometrium, 2 of solitary endometrial cysts—one of which strongly resembled pregnancy, 2 cases of muco-metra and 2 of pneumometra. The cervix was free from abnormalities."

Dr. T. D. Glover (Cambridge). "There is considerable evidence in bulls of a relationship between sexual arousal and the volume and quality of semen ejaculates. I am wondering if the possibility of this relationship is sufficiently recognised in Thoroughbred studs. Sexual excitation is, for instance, an important feature of natural mating, and yet I understand that in many cases, so as to preserve a valuable stallion from being picked by a mare not fully in oestrus, teasing is carried out by a horse of poorer quality, a vasectomised or infertile animal. Yet it would seem that the very act of 'teasing' might markedly influence the stallion's semen quality. Could Mr. Day please comment on this matter?"

Mr. J. S. Steward (Nottingham) asked the significance of a thin milky uterine discharge. He also asked for the prognosis in respect of the breeding of mares with a tight cervix with or without oestrus. He also asked whether abortions had followed phenothiazine therapy.

Mr. L. W. Mahaffey (Newmarket). "As usual Mr. Day has presented us with a great number of facts based upon an exceptional experience in this field. I should, however, like to mention one or two things. Several years ago I brought up the question of the real value of luteinising hormone in hastening ovulation when an apparently suitable follicle was present in the ovary. I was not satisfied then, as I am not now, that there was enough evidence to place as much faith in this substance as Mr. Day does. The great variability in the time of ovulation and the extreme difficulty in predicting this event in any instance make it quite a formidable task to set up a reasonable experiment which might have a chance of giving statistically satisfying results. I used the hormone clinically during 5 consecutive foaling seasons in Australia and the results seemed to be all over the place so that both my client and myself could not but lose faith in the injections. Further, I think Mr. Day uses the hormone as a last resort towards the end of the season when ovaries are functioning well anyway and when the obstinate cases of hanging fire and regression are becoming less common. I intend to remain sceptical on this matter until figures which can be critically analysed become available.

"Mr. Arthur's contribution is very valuable; 792 *post-mortem* examinations of mares are quite a lot and will make interesting reading when his paper appears. I agree with him on the scarcity of true cysts and there is little doubt that organs other than the ovary are responsible for manifestations of oestrus because intense heat is fairly frequently seen in any one season in certain mares with very tiny ovaries. One presumes the adrenals are concerned in this."

Mr. J. S. Cosgrove stated that all brood mares are examined and cervical swabs frequently reveal streptococcal or staphylococcal infection frequently resistant to antibiotics. He deplored the treatment and neglect of barren mares, and felt that they should be as well taken care of as in-foal mares. This would help to get early foals.

A routine ovary examination before each service would prevent serving with twin ovulation.

Mr. A. E. Carey Foster (Lingfield) pointed out that at Lexington, U.S.A., they tended to use luteinising hormone prolifically, but its action seemed to be unreliable. He wanted to know what steps were being taken to answer that it was absolutely effective. He pointed out that open ovary gave much higher fertility rates and that "Nature is still a long way ahead of us."

He also asked what is the factor in grass which is such a stimulant to reproductive activity at certain stages? What work is being done in this connexion?

Mr. Day had pointed out the shedding of the coat which accompanies improved ovarian behaviour. In Kenya cows which have recovered from foot-and-mouth disease seem to suffer from pituitary disfunction. They show nymphomania and grow shaggy coats like white Highland cattle. With the growth of corn grass—presumably vitamin A—the animals get better, their coats improve and ovarian function returns.

The Chairman (Mr. F. G. Waddington): "Before asking Mr. Day to reply to the points raised in the discussion, I would like to comment on one small point in his paper. He refers to coat-shedding as an indication of improved ovarian action. Some years ago, in East Africa, I was in charge of an outbreak of foot-and-mouth disease and there we allowed the animals to recover and so saw the disease run its natural course. The pathologists told us that one of the effects of foot-and-mouth was a degeneration of the pituitary gland, which they had proved by making sections from affected animals which had died. When the cattle recovered from the acute disease it was common to see that many of them grew long, shaggy coats like Highland cattle. This, of course, was the outward and visible sign of the pituitary degeneration. I had the opportunity of examining the ovaries of 30 or 40 cows which were recovering from foot-and-mouth and did so every 3 days for a period. It was then evident that the ovarian cycle was completely out of step; and I note cystic ovaries, persistent corpora lutea, delayed ovulation and small anoestrus ovaries.

"Some of these cows also showed the increased growth of their coats, and it was noted that with time—and improvement of grazing with the advent of the rainy season—the ovarian activity settled down to normal and concurrently, in those cows which did improve in this manner, the long coat was shed and the outward appearance returned to normal."

The Reply

Mr. Day, replying to the discussion, said first that Mr. Haselden had not thought the 30-day examination a practical procedure, but Mr. Day pointed out the emphasis he had laid on the fact that the routine examination and diagnosis was not recommended until 40 days. There were, however, certain circumstances towards the end of the season when a slightly earlier examination could help materially. If one was always doing the job and was able to give the answer it would be unwise to disregard the odd occasions when earlier examination could be helpful. The danger of washing out a foetus was very real and the more time that could be given the better; but the chance of washing out a foetus at 6 weeks was remote.

It was difficult to say how much ovary checking was necessary and how much could be left undone. The veterinarian very rarely had all the time in the world at his disposal for checking with the individual stud groom. Very often he was called to the stud on certain days of the week and had to deal with a group of mares. With 40 or 50 mares to a stallion the best use had to be made of the time available. The suggestion came from the stud as to which mares should be examined.

The distance from the stud in relation to the checking of mares was giving a lot of worry to the people at Lexington where, of course, the distances to be travelled were so very much greater. Mares with bad breeding histories should certainly be checked, and working closely with the stud groom was very important. Mares which had to travel long distances to be covered presented a very tricky problem. He (Mr. Day) had checked some at their home bases and found them just as they should be, but after travelling 50 or 60 miles they would not accept the stallion because they had been left so near to ovulation. To take them, perhaps, 60 miles to be covered, leave them in a box for a couple of hours, and then take them back again was quite an impossible thing to do, and the mares were upset.

Dealing with twin ovulations, Mr. Day thought Mr. Haselden had given a wrong impression when he spoke of leaving one follicle but not being sure of not getting twins. He could be sure if the covering was after the time of complete ovulation. In his paper, Mr. Day said, he had emphasised the interesting feature of a slightly induced ovulation, where the right follicle was pressed down. With a 2-hour interval after the pressing down he had got pregnancy but had not got it when ovulation was complete. Mr. Haselden had described his excellent "blunderbuss" treatment, where he had inseminated the mares, and stitched them up. Having mares covered then stitched up was frequently done and it very often worked. There was nothing against the procedure. Removal of an ovary *per vagina* depended, of course, on the relative sizes. A stilboestrol implant could be helpful in the case of tumours. Where there was an ovarian tumour the other ovary was always tiny. Normally, he would say that nothing bigger than a grapefruit could be taken *per vagina*.

Mr. Day said that, luckily, he had not had much trouble with post-operative haemorrhage, but went on to describe one such case in his own experience. He could not agree with Mr. Haselden on the question of prolapse of the uterus. Fortunately, that was of low incidence in Thoroughbreds, but Mr. Haselden would make his whole procedure much simpler by the use of up to 10 c.c. of epidural. He quite agreed that it was essential to get the horns of the uterus out the right way, but it was a very difficult thing to do completely. Epidural was very easy to give and it immediately cut out straining and made a comparatively simple job.

Testing for fertility was undoubtedly difficult, but Mr. Haselden had not given a good example to illustrate his point. He had given an impression that the stallion was suffering from delayed maturity. In that particular case there was every reason to hope that time would provide a satisfactory answer, and the fact that it had was not surprising. He himself had seen at least two horses which

had given very poor fertility results all their lives but which he would have reported favourably had he tested them for fertility. One could go only on service behaviour, volume and density of semen and initial fertility. At the moment there were no other tests that could be used. He could, if necessary, instance two horses which he would have reported as satisfactory on test but which proved rather poor getters at stud.

He could not agree with Mr. Arthur's statement that clinical examination could not reveal the contents of an ovary. He was quite right in the case of the immensely large ovary, the one blown up with a multitude of follicles. Nobody could tell what was the matter there, but with most ovaries it was possible to be fairly sure of the contents. Mr. Day referred to large follicles as that aspect came into early pregnancy diagnosis. At anything from 40 to 100 days, pregnant mares did blow up very large follicles, and his experience of ovariectomy for nymphomaniac mares had been the same as Mr. Arthur's. It was not, however, a true nymphomania, and did not often have any relationship to the state of the ovaries.

Twin ovulation was of much greater incidence in the heavier breeds than in the Thoroughbred. In Thoroughbreds he would put the figure at nearer 10 per cent. than 5. His own experience was that when aware of twin ovulation and both eggs had had a chance of fertilisation he was not disappointed to feel twins at the end of 6 weeks. Occasionally they were lucky and only felt one foetus. As in all animals resorption was occurring at all levels, but they were aware of the big percentage of resorption at 30 and 40 days' pregnancy.

Did luteinising hormone work? It did if there was more than one follicle of a size that it could "hit off."

Mr. Day thought that when Dr. Glover had mentioned excitement of the stallion he had in mind the bull, where it was essential to provide a period of excitement prior to ejaculation because in that case the whole act of service was so quick. Mr. Day did not think it was so important with the stallion, whose act of service was so much longer, and he did not think that there was any evidence to suggest that on the average stud there was any insufficient stimulation of the male. There was, however, great variation in stallion behaviour. Some horses were lethargic and slow and took a long time to serve but, once served, the mare was in foal. Others "went off like a squib" and were also fertile. Mr. Day liked to see stallions stay on their mares and lose their erection completely and not very quickly so that the penis dropped away. Where they drew away quickly, a large amount of semen was lost on the floor.

The cysts that had been mentioned were not really attached to the ovary as such but were on a little membrane. Clinically, not a lot could be felt as they were so soft and had not the necessary degree of tenseness for palpation. Only the big ones could be felt, but those did not appear to play any part in fertility at all. They were just something left over from the early days and remained unchanged. Mr. Day thought that oestrus in late pregnancy was quite exceptional. It did occur in the occasional mare, and that mare continued to show it throughout her life.

Mr. Steward had mentioned "milky discharge"—a horrible thing to meet. One came across it in the mare that had been left unstitched and sucking in air for a long period. In the mares Mr. Day had mentioned it was almost like a pyometra, where the cervix was normal but the uterus partially filled up with the discharge. More often than not it occurred in cases where the ovaries were not normal as to shape and size and consistency, but he himself could not understand it. It was wretched to see such mares. At the same time, some of them did get in foal again, though he himself would not like to buy one.

They were always cautious in the use of phenothiazine in the treatment of abortion but had gained some confidence in its use. He had seen only one mare really ill, and she was jaundiced and off her feed for a week. Ponies that were not used to being handled could be made to abort through sheer fright.

In reply to Mr. Mahaffey, Mr. Day could not quote any published work or produce any evidence that would satisfy him if what had already been published on the use of luteinising hormone had not done so. However, if Mr. Mahaffey would send him a batch of the stuff he wanted testing he would tell Mr. Mahaffey if it worked with mares. With bad material virtually nothing happened, but effective material proved successful at least 7 times out of 10. Mr. Mahaffey was completely wrong in saying that it worked better at the end of the season than at the beginning. It was used throughout the season.

Mr. Day was at a loss to know how the word "cyst" had come to be used in regard to mares. When it was said that a mare had a large cyst it did not mean that at all. It was a follicle out of gear.

Enterotoxaemia of Sheep

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ENTEROTOXAEMIA of sheep, or pulpy kidney disease, is still one of the major causes of loss among sheep and lambs, both in this country and abroad. Bennetts (1932), in his original account of the disease, stated that annual losses in Western Australia varied between 1 and 29 per cent.; losses of 5 to 15 per cent. being quite common. Heath (1955) described the results of 530 consecutive *post mortems* made at Bangor during 1953-4 and showed that enterotoxaemia killed more of the sheep and lambs examined than any other individual disease, and was responsible for 152 of the 530 deaths, nearly 29 per cent. Menzies (personal communication) states that 508 cases of enterotoxaemia were found among the 5,518 sheep, lambs, or sheep viscera sent to 16 Veterinary Investigation Centres during the year ending September 30th, 1956.

The figures given by Heath and Menzies do not show the total incidence of the disease as each case sent for diagnosis may represent many dead animals in a flock. They do indicate, however, that the disease is a common cause of death amongst sheep in this country at the present time.

These severe losses continue in spite of the extensive use of suitable antisera and vaccines. It seems clear that our failure to control enterotoxaemia is due partly to our lack of understanding of its predisposing causes. Similar views were expressed by several speakers in the discussion of a paper on the prevention of enterotoxaemia by Montgomerie and Thomson at the B.V.A. Congress in 1954.

We have attempted to investigate some of these predisposing causes in the hope that a better understanding might lead to more efficient methods of control. Vaccines and sera can play a vital rôle; nevertheless, more consideration should be given to animal management, especially with regard to feeding.

Source of Infection

Bennetts (1932) considered that the infection was derived from contaminated pasture or soil. In his view the disease could occur only if the ingested organisms survived the passage through the rumen and abomasum and reached the small intestine in sufficiently large numbers to become established and produce toxin. Gill (1929) and Oxer (1932) suggested that the organism might be a common inhabitant of the alimentary tract of normal sheep, either as part of the established flora or as a frequent and usually harmless contaminant of the gut contents. The disease might then occur whenever the environmental conditions in the gut became suitable for rapid multiplication of the bacteria.

Until recently there were only a few records of the isolation of *Cl. welchii* Type D from sources other than sheep dead of enterotoxaemia. Bennetts isolated the organism from the abomasum of two healthy sheep in an area where the disease had occurred. Taylor & Gordon (1940) isolated a few strains from the soil, the intestinal contents of a sheep, a cow, and a rabbit. Borthwick (1937) found the organism in three guinea-pigs and two dogs.

We now have evidence that *Cl. welchii* Type D may be present in the alimentary contents of large numbers of normal sheep. The organism was detectable in the alimentary contents of 46 of 100 normal sheep sent to a Cambridge slaughter-house over the period of a year (Bullen, 1952). Samples of alimentary contents were sown into small quantities of papain digest broth. After incubation the culture filtrates were tested for epsilon toxin. *Cl. welchii* Type D were readily isolated from 12 mixed cultures selected at random which contained epsilon toxin. These results are summarised in the table. If these results are typical for sheep populations wherever the disease occurs, it seems likely that enterotoxaemia may develop whenever the environment in the gut becomes suitable for rapid multiplication of the organisms. It was also found that the distribution of *Cl. welchii* Type D among the 100 animals was very uneven.

TABLE

TOTAL NUMBER OF CULTURES CONTAINING EPSILON TOXIN OBTAINED FROM DIFFERENT SITES IN THE ALIMENTARY TRACTS OF 100 NORMAL SHEEP.

Site	Number of Cultures	
	Examined	Containing epsilon toxin
Rumen	89	19
Abomasum	99	15
Duodenum	100	14
Jejunum	100	17
Ileum	100	30
Colon	100	22
Totals ...	588	117*

* The 117 cultures containing epsilon toxin were obtained from 46 of the 100 sheep examined.

In some groups the organism was present in almost every part of the gut examined, in some groups it was present only occasionally, in others all the

cultures were negative. It thus seems likely that some flocks are more heavily infected than others. This is one factor that may help to explain the uneven distribution of the disease.

Experimental Reproduction of Enterotoxaemia

The Effect of a Single Dose of Culture into the Rumen

Several workers have attempted to reproduce enterotoxaemia in normal sheep. Bennetts (1932) found that oral doses of culture were without effect. He suggested that a low *p*H in the abomasum might destroy large numbers of ingested organisms, and that the rapid passage of ingesta through the small intestine would prevent any accumulation of bacteria and toxin. He therefore attempted to reduce peristalsis in the intestine with large doses of opium and belladonna. He reproduced the disease in four of six sheep. Oxer (1932) and Gill (1933) failed to repeat these results. Roberts (1938) reproduced the disease in young lambs by feeding culture combined with large quantities of milk powder and casein. In these circumstances the organisms grew well in the abomasum. Unfortunately it is not known if the organisms that passed into the intestine continued to grow and to produce toxin or whether a sufficient dose of toxin accumulated in the abomasum and was absorbed lower down the intestine. Shaw *et al.* (1939) failed to reproduce the disease in lambs with large doses of culture and sodium bicarbonate, or with culture and a large feed of milk. Harshfield *et al.* (1942) apparently reproduced the disease in three of eight lambs given culture and large feeds of grain or milk. These experiments do not help very much to explain the pathogenesis of enterotoxaemia, although they show that the mere presence of *Cl. welchii* Type D in the intestine is insufficient to produce the disease.

The apparent resistance of normal sheep to large doses of culture of *Cl. welchii* Type D suggested the presence of highly efficient defence mechanisms.

It was felt that investigation of these defence mechanisms might provide some clue to the circumstances which could favour the rapid growth of *Cl. welchii* Type D in the gut. Experiments were therefore designed to follow the fate of *Cl. welchii* Type D introduced into the rumen (Bullen *et al.*, 1953). Sheep were equipped with permanent fistulae in the rumen, duodenum, and ileum. Large numbers of *Cl. welchii* Type D were introduced into the rumen and viable counts were made at frequent intervals from samples of alimentary contents removed through the cannulae.

It was also necessary to have some method of estimating the flow of the contents of the alimentary tract, as this would greatly influence the viable count. Some experiments were done in which an insoluble radio-active marker with suspension properties similar to that of *Cl. welchii* was introduced into the rumen simultaneously with the bacteria. The marker consisted of a trace of iridium 192 incorporated into particles of alumina. The behaviour of the bacteria could then be compared with the flow of these particles. The concentration of the marker could be measured with an accuracy of measurement to within 2 per cent. for the first 18 hours of an experiment. It was found that the concentration of the organisms introduced into the rumen was halved in approximately 1.6 hours whereas 15 to 16 hours were required to halve the concentration of the marker particles. The results for the marker agree quite well with those recorded for other types of insoluble material such as chromic oxide (McDougall, 1944). It was calculated that about 90 per cent. of the original dose of the organisms was destroyed in the rumen. This appeared to be one good reason for the failure of oral doses of culture to reproduce the disease. Similar observations showed that a large proportion of the surviving organisms were destroyed before they reached the duodenum.

In spite of these severe losses a number of viable bacteria reached the small intestine. These multiplied extremely rapidly. In one experiment the ratio of bacteria to marker in the rumen after one hour was approximately 6,000 to 1. By the time the organisms had reached the duodenum the ratio was less than 100 to 1, yet after three hours the ratio of organisms to marker in the ileum was approximately 250,000 to 1. Nevertheless, this high rate of multiplication was not maintained, and the ratio had dropped to 800 to 1 after 15 hours. These experiments showed that although *Cl. welchii* Type D could grow rapidly in the intestine, the rate of multiplication was insufficient to maintain their numbers. Thus the normal rate of flow of intestinal contents appeared to be another powerful defence mechanism which helped to prevent the development of the disease.

It was also found that considerable quantities of epsilon toxin, usually several 100 mouse MLD per gramme, were produced when the organisms were multiplying in the intestine. These concentrations of toxin appeared to be harmless.

The Effect of a Continuous Dose of Culture into the Duodenum

In order to increase the concentration of bacteria in the intestine a continuous drip of culture was introduced into the duodenum for a number of hours (Bullen & Scarisbrick, 1957).

The culture contained about 500 to 800 $\times$ 10^6 organisms per ml. and was usually introduced at the rate of 100 ml. per hour for some five to seven hours. Occasionally larger volumes, up to 300 ml. per hour, were given for as long as 27 hours. Normal sheep proved to be unexpectedly resistant to this treatment (Fig. 1). Some animals showed no symptoms of any kind, others developed short attacks of diarrhoea. The maximum viable counts in the ileum varied between 1 and 700 $\times$ 10^6 organisms per gramme with epsilon toxin concentrations of several 100 mouse MLD per gramme. In one experiment a culture containing 650 $\times$ 10^6 organisms per ml. was dripped into the duodenum for 22 hours at the rate of 300 ml. per hour. For a very short period the toxin level reached 8,000 MLD per gramme, but for most of the time varied between 80 and 800 MLD per gramme. The animal developed diarrhoea but otherwise remained normal.

XUM

The Effect of a Change of Diet

A sheep depends upon the microflora established in its rumen for digestion of its food. If the diet is changed suddenly, from hay to wheat for example, some time elapses before the rumen flora becomes adapted to the new environment. If the sheep also overeats on the new diet considerable quantities of undigested or partly digested food escape into the small intestine. When wheat, oats, or maize were fed under these conditions, the intestine became filled with a mass of starch granules. In this environment *Cl. welchii* Type D grew extremely rapidly. In a few hours the viable count rose to over 1,000 × 10^6 organisms per gramme, and these numbers were maintained or increased in spite of the development of a profuse diarrhoea. The rapid growth was accompanied by high concentrations of epsilon toxin in the intestine, up to 20,000 mouse MLD per gramme. These conditions were not tolerated for long and the sheep soon died from acute enterotoxaemia (Fig. 1).

In our experiments there was a good correlation between the appearance of starch granules in the intestine and the successful reproduction of the disease. If, for example, the new diet was fed slowly, the rumen flora had time to adapt itself to the new conditions, and no free starch was seen in the intestine. Organisms introduced into the duodenum failed to grow well and the animal survived.

The Absorption of Clostridium welchii *Epsilon Toxin from the Intestine*

One of the most interesting aspects of enterotoxaemia is the absorption of *Cl. welchii* epsilon toxin

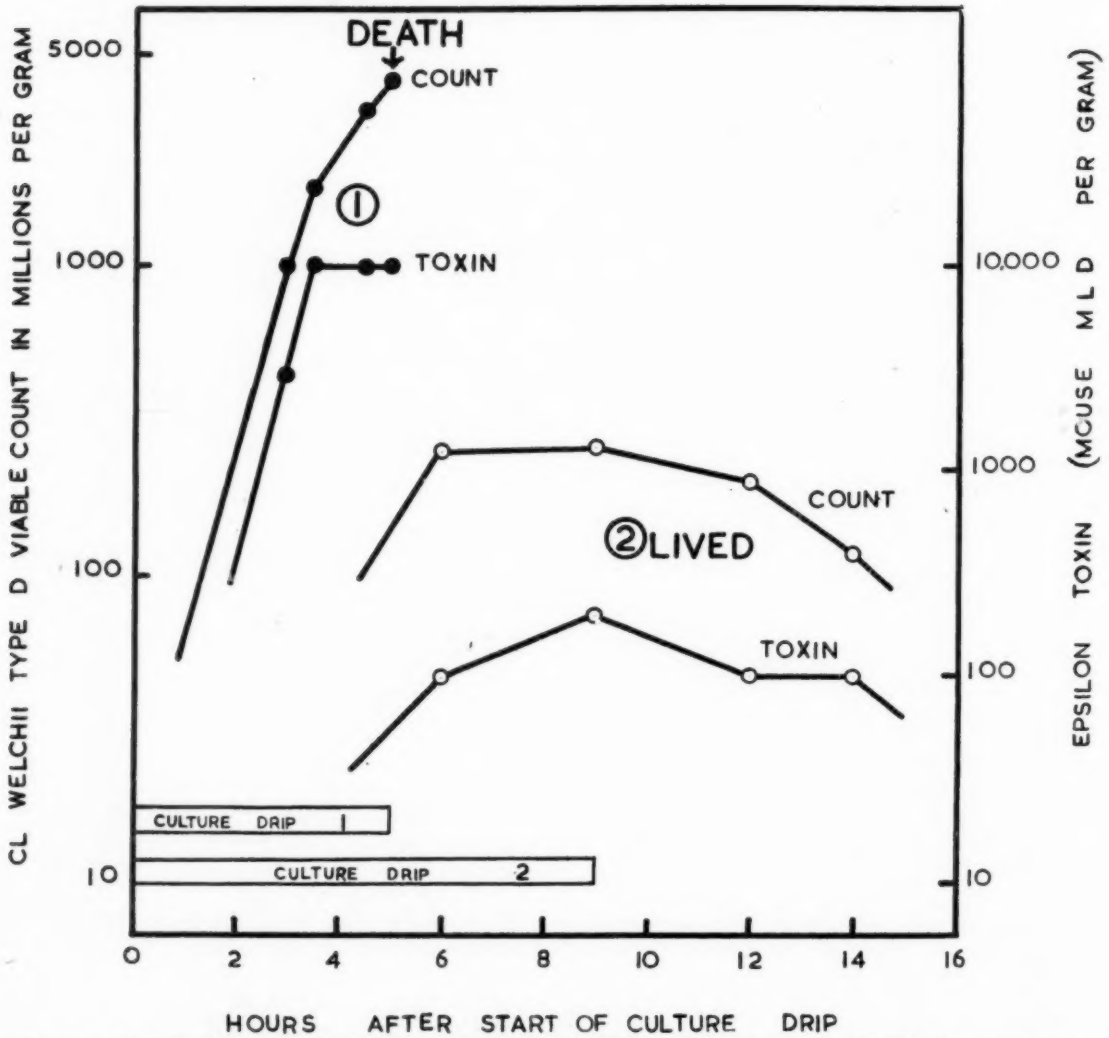

FIG. 1. — Growth of *Cl. welchii*, Type D and production of epsilon toxin in the ileum. (1) Experimental enterotoxaemia. Sheep over-eating on wheat. (2) Unsuccessful attempt to reproduce enterotoxaemia. Sheep on hay diet.

from the intestine. The size of the toxin molecule is not known, but it is unlikely to be much smaller than a molecule of haemoglobin as it is retained by collodion membranes which retain haemoglobin. The toxin is not absorbed easily, as both sheep and mice can tolerate low concentrations for long periods. Nevertheless, lethal amounts of toxin are quickly absorbed if high concentrations are maintained in the intestine for several hours. We have shown that high concentrations of toxin rapidly increase the permeability of the intestine (Bullen & Batty, 1956, 1957). This was done by observing the effect of toxin on the rate of absorption of antibody globulin from the intestine. If large amounts of antibody globulin are introduced into the normal intestine, very small amounts are absorbed into the blood, showing that the intestinal wall is very slightly permeable to this protein. In the presence of high concentrations of epsilon toxin the rate of absorption of antibody is much faster than normal showing that the permeability of the intestine is increased.

Concentrated culture filtrates of *Cl. welchii* Type D were used for experiments in mice. Epsilon toxin appeared to be responsible for a rapid increase in permeability and some other factor or factors responsible for a delayed increase in permeability. In both sheep and mice there was an appreciable increase in permeability before the animals showed any signs of epsilon toxin poisoning.

Experiments with immune sheep showed that high levels of circulating epsilon antitoxin gave very good protection against the experimental disease. One animal which had 5 to 10 units of antitoxin per ml. of serum survived a toxin concentration in the ileum of 10,000 to 20,000 mouse MLD per gramme maintained continuously for 10 hours. Apart from a severe mucoid diarrhoea the animal remained normal. Some toxin was apparently absorbed as the animals developed a typical secondary response to the epsilon antigen with a rapid increase in the amount of circulating antitoxin.

Symptoms and Post-mortem *Changes in Experimental Enterotoxaemia*

Ten sheep were killed with experimental enterotoxaemia. Seven died between five and nine hours after the start of the culture drip, one died after 12 hours, another after 15 hours. The last animal took 27 hours to die; the delay being due, in all probability, to the protective effect of a low level of circulating epsilon antitoxin.

Most of the animals showed typical nervous symptoms which appeared between half and one and a quarter hours before death. The most striking abnormality was the development of a marked hyperglycaemia which was always closely associated with typical symptoms of the disease (Fig. 2). These observations agree well with those of Gordon *et al.* (1940) who found that the injection of lethal doses of *Cl. welchii* Type D filtrates produced a marked hyperglycaemia while filtrates of *Cl. welchii* Types A and C did not produce this effect. These workers also found that the urine of natural cases of enterotoxaemia contained large quantities of sugar. Glycosuria has also been reported in natural enterotoxaemia in the United States (Boughton & Hardy, 1941).

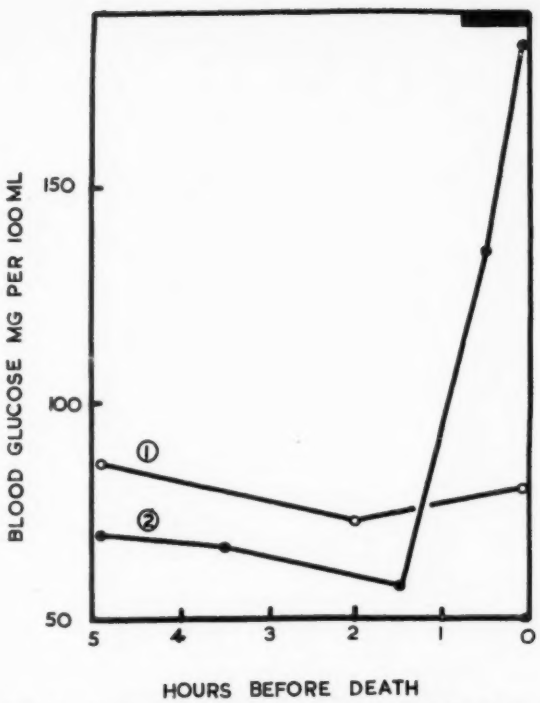

FIG. 2.—Blood glucose levels in one sheep dying from "acidosis" (1) and one sheep dying from experimental enterotoxaemia (2).

■ Symptoms of enterotoxaemia.

Nine of the 10 animals were examined immediately after death. Except for the presence of gas in the intestine and sugar in the urine, very few abnormalities could be found, although a number had a large excess of clear fluid in the pericardial sac. One animal examined 12 hours after death showed the typical pulpy kidney lesion.

Enterotoxaemia and Overeating

A sudden change of diet and overeating appeared to play an essential part in the experimental reproduction of enterotoxaemia. Overeating by itself, however, can cause illness and sometimes death in normal sheep (C.S.I.R.O. Reports, Australia, 1949, 1950, 1951, 1952; Hungate *et al.*, 1952, and Scarisbrick, 1956). If the diet is suddenly changed from hay to wheat and the sheep overeats, the rumen soon becomes acid. This is due to the rapid multiplication of certain normal inhabitants of the rumen, usually *Streptococcus bovis*. These acid-producing organisms soon replace the normal rumen flora. After 12 to 24 hours the animals may show symptoms of acidosis characterised by lethargy and inappetence and in more severe cases by hyperventilation, salivation, occasional grunting, and grinding of the teeth. The *p*H of the rumen may fall to between 4.0 and 4.5. Death may occur some 24 to 72 hours after feeding.

Australian reports (C.S.I.R.O., Fourth Report, 1952) showed that the acidosis produced by feeding with wheat could be prevented by dosing the animals with chlortetracycline. We found that penicillin was equally effective. Five normal sheep were given large doses of wheat and penicillin introduced into the rumen. The *p*H of the rumen remained much higher than normal and none of the animals showed any symptoms of acidosis (Bullen & Scarisbrick, 1957).

The fact that sheep could die from acidosis after large feeds of wheat made it essential to distinguish this syndrome from experimental enterotoxaemia. Sheep dying from acidosis showed symptoms of dullness and inappetence, followed by sudden collapse shortly before death or a prolonged weakness and prostration with hyperventilation and salivation followed by coma and death. Most of the animals dying from enterotoxaemia showed typical nervous symptoms with convulsions. The interval between the appearance of typical symptoms and death was short, not more than one and a quarter hours. Of the 10 animals killed with experimental enterotoxaemia five showed no symptoms of acidosis. In three animals the fall in *p*H in the rumen was prevented by dosing the animals with sodium bicarbonate or penicillin. In two fed on lucerne or small quantities of oats no symptoms of acidosis developed. The remaining five animals showed only mild symptoms of acidosis and three died within six hours of the start of the culture drip. Finally, 9 of the 10 dying of enterotoxaemia (one was not examined) showed a well-marked hyperglycaemia closely related to typical symptoms. All the animals dying from acidosis showed normal blood glucose levels shortly before death (Fig. 2).

Prevention of Enterotoxaemia

Two means of prevention are possible and wherever practicable should be used simultaneously. Every attempt should be made to avoid a sudden change from a poor diet to a rich one. Changes of diet should be made gradually and the animal prevented, if possible, from overeating. We know that high levels of circulating epsilon antitoxin will protect an animal from high concentrations of toxin maintained in the intestine for several hours. Suitable vaccines and sera should therefore give complete protection provided the level of antitoxin in the blood is adequate, at least 0.1 unit per ml. of blood. Smith & Marsh (1953), state that 0.3 unit per ml. gives adequate protection and that it is probable that lower amounts may be sufficient.

Repeated vaccination is more likely to give satisfactory results, and the last series of injections should be timed to provide a maximum antitoxin response when the animals are exposed to the effects of a change of diet. With valuable flocks it would probably be worth-while to bleed the sheep during the course of immunisation to ensure that the flock as a whole was developing an adequate level of antitoxin. The choice of vaccine and methods of use are also important (Batty *et al.*, 1954).

Discussion

The following tentative hypothesis is suggested to explain the development of natural enterotoxaemia. It would appear that *Cl. welchii* Type D is frequently present in the intestine of normal sheep, although it seems that some flocks may be more heavily infected than others. The organisms cannot grow sufficiently rapidly in the normal intestine to produce disease even if introduced artificially in very large numbers. Two factors, in particular, have a powerful restraining influence on the growth of the bacteria. First, the rapid flow of the intestinal contents. Secondly, the absence of large quantities of fermentable substrate. It will be seen that each of these factors reinforces the effectiveness of the other.

If, however, the normal feeding habits of the sheep are upset by a sudden change of diet followed by overeating, large quantities of undigested or partly digested food escape into the intestine from the rumen. This undigested food provides an ideal substrate for extremely rapid multiplication of *Cl. welchii* Type D. The rate of growth is so fast that even a profuse diarrhoea has little effect on their numbers. This rapid growth is accompanied by the production of high concentrations of epsilon toxin. Low concentrations of toxin are harmless, but high concentrations, if maintained for a few hours, rapidly increase the permeability of the intestine. Large quantities of toxin are absorbed and the animal dies from acute enterotoxaemia.

Summary

Enterotoxaemia is a common cause of death among sheep. The organism responsible for the disease, *Clostridium welchii* Type D, is a common inhabitant of the alimentary tract of normal animals.

The disease cannot be reproduced in sheep fed on normal diets such as hay even if large quantities of culture of *Cl. welchii* Type D are introduced into the intestine for long periods of time. This appears to be due to the following factors: the absence of large quantities of fermentable substrate in normal intestinal contents limits the growth of the organisms; the rapid flow of the intestinal contents soon removes any accumulation of bacteria and toxin; the toxin is not easily absorbed and low concentrations are harmless.

The disease can be reproduced consistently if the diet is changed suddenly and large quantities of rich food such as wheat are eaten before the culture is introduced into the intestine. In these circumstances the rumen flora cannot adapt itself sufficiently rapidly to the changed environment and large quantities of undigested or partly digested food escape into the small intestine. This provides an ideal substrate for *Cl. welchii* Type D which grow extremely rapidly and produce high concentrations of epsilon toxin. High concentrations of toxin and possibly other metabolic products of the bacteria rapidly increase the permeability of the intestine. Large quantities of toxin are absorbed and the sheep dies of acute enterotoxaemia.

Experimental enterotoxaemia can be distinguished from death due to acidosis which can follow overeating on diets such as wheat.

Losses due to enterotoxaemia could be more adequately controlled by avoiding sudden changes of diet and preventing sheep from overeating, and also by adequate vaccination designed to ensure high levels of circulating *Cl. welchii* epsilon antitoxin.

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THE SPEAKER'S INTRODUCTION

Dr. Bullen said that the intention in the paper was to give a summary of the past 5 years' work, but he desired to point out that there had been many other colleagues concerned with the work of enterotoxaemia of sheep, particularly Dr. R. Scarisbrick.

Dr. Bullen then showed a number of slides, the first of which concerned the carrier state in sheep. He said that 100 normal sheep were examined over a year at Cambridge, 5 at a time, and the organism was found in various parts of the intestines. Nearly 50 per cent. of the animals were found to be carriers of the organism, and the groups varied greatly in the carrier rate. It was felt that it might, in part, account for irregular distribution of the disease.

The next part of the work concerned an attempt to reproduce the disease. One slide showed a measure of the viable count in the ileum. It was found that if the animal's diet were changed suddenly, an entirely different picture resulted. Instead of the organisms growing for a reasonable length of time at a steady level, there was a constant increase at a very rapid rate. This was due to the presence of undigested or partially digested food in the intestine. On a normal diet such as hay the rumen flora consists almost entirely of cellulose digesting organisms. If the diet is suddenly changed, to wheat, for example, large quantities of fermentable carbohydrate enter the rumen and this new material cannot be digested by the existing flora. In time a new flora capable of digesting wheat will grow up to replace the old, but in the interval, undigested food escapes into the intestine. This provides an ideal substrate for *Cl. welchii* type D.

Slides were then shown illustrating the predisposing causes of enterotoxaemia.

The Opener

Mr. W. T. Rowlands, in opening the discussion, said that many among those present would realise that he had a special interest in the subject of the paper, having played a small part, together with Dr. Montgomerie, in the original investigations into the disease in lambs and adult sheep, which served to confirm that the disease described under the heading of enterotoxaemia or pulpy kidney disease by investigators in Australia and New Zealand also occurred in Great Britain. The work showed that it was due to the toxic produced by the rapid proliferation of *Cl. welchii* type D in the bowels of sheep, although toxin could not be detected in a high proportion of cases of the disease as diagnosed. Although it was assumed at that time that the natural mode of infection was by ingestion of the causative organism, no real success attended attempts to reproduce the disease experimentally in that manner. However, subsequent successful prevention of the disease in the field with specific antiserum or vaccine fully confirmed the part played by the bowel toxin in the causation of the disease.

Even so, until the experimental reproduction of the disease could be successfully achieved, one had to be content to accept the symptoms and *post-mortem* picture seen in field cases of the disease to be, in fact, diagnostic of enterotoxaemia.

To-day, as the result of the efforts of the authors it was now possible to determine those factors specifically, for they reported the successful reproduction of enterotoxaemia experimentally. They had thus satisfied a long-felt need to clarify many points of importance connected with the problem.

As a result of that work it was possible to discuss certain matters concerning the problem of enterotoxaemia. The work confirmed, for example, previous observations that the mere presence of *Cl. welchii* type D, or indeed, of its specific epsilon toxin even in considerable concentration was not itself able to cause clinical disease. It would appear that before that could happen the presence of a sufficient concentration of toxin over a sufficient period of time was essential in order to increase thereby the permeability of the bowel mucous membrane. There was thus an explanation as to why *Cl. welchii* type D could often be isolated from the bowel contents of apparently normal sheep. It might well explain also the finding of epsilon toxin often in high concentration in the bowel contents of sheep dying from some totally different cause, for example, Black Disease. It would be interesting to know whether the authors had come across such cases.

The authors stated that the work was undertaken because of "the continued severe losses in spite of the extensive use of suitable antisera and vaccine," and "in the hope that a better understanding might lead to more-efficient methods of control," which they concluded could be more adequate "by avoiding sudden changes of diet and preventing sheep overeating and also by adequate vaccination designed to ensure high levels of circulating *Cl. welchii* epsilon antitoxin."

As matters stood to-day the shepherd was reasonably well safe-guarded against the sale of inefficient biological products, official standards having been fixed for such products. Was there any evidence that much inefficient material was marketed to-day? At the same time apparent

failures of otherwise efficient products might be explained in one or two ways. It was now widely accepted that shepherds could obtain those biological products freely through chemists and without recourse to professional advice. The efficient use of those products in those and in all circumstances presupposed two things: (a) that the immunological nature of a serum and of a vaccine was clearly understood and differentiated, and (b) that a correct diagnosis had been made of the cause of the losses one was attempting to prevent.

He desired to deal with those two matters—the efficient use of biological products briefly and diagnosis in some detail—in the light of the information presented by the authors. It must, however, be made clear that he spoke from the limited experience of conditions as they applied in North Wales, and in relation to diagnosis with reference only to enterotoxaemia in the ewe.

With reference to the efficient use of biological products, there was no reason to go into detail over that as it was the subject of an excellent paper by Montgomerie and Thomson at the 1954 Congress, and by Mrs. Batty and her colleagues in THE VETERINARY RECORD of the same year. It was questionable whether shepherds without professional advice possessed a proper appreciation of the true immunological action of a serum or a vaccine. Thus the use of serum where vaccine was better indicated or vice versa was commonplace, and there was no need to pursue the point further. Again, little was known by the shepherd of the period of protective cover offered by a serum or a vaccine and disappointment often followed their use for that reason. The authors had indicated that a certain level of circulating antitoxin must be present if a satisfactory immunity were to be achieved. He suggested therefore that the misuse of those products in that manner might explain, at least in part, the reason for the continued high incidence of enterotoxaemia " in spite of the extensive use of suitable antisera and vaccines."

The question of diagnosis of enterotoxaemia in the ewe, if the issue were honestly faced, was one which, in his submission, must cause even the qualified veterinary surgeon some anxiety. It was easy to understand how readily a shepherd could go wrong. Differential diagnosis was a matter of major concern—at least to those in North Wales, and considerably more food for thought in that connexion had been presented by the authors of the paper. There was very much concern in North Wales about the general increasing incidence of what, in ignorance, was called metabolic disorders among sheep associated with improved grassland. That concern was related both to the direct losses concerned to agriculture and to the difficulties those disorders presented in the matter of differential diagnosis, for they seemed to follow a pattern closely resembling enterotoxaemia.

In making a diagnosis of any disease condition one took into consideration the history or background (including management), symptoms, *post-mortem* findings, and any other additional laboratory findings. Until the presentation of the paper, all those factors had been related to what had been assumed to be cases of enterotoxaemia. Thus the disease was associated with a history of a sudden change to a better diet, either by regulated movement of the flock as part of management or more often induced by a change in weather conditions. Symptoms were usually few, consisting of vague nervous symptoms, but death was generally sudden. Losses occurred mainly in spring and early summer when ewes were normally lactating. Thus far there was little in the background that was different from that associated with acute metabolic disorders. The difficulty of differential diagnosis became acute if the only factual evidence was a dead sheep. The widely accepted *post-mortem* picture consisted of an excess of pericardial fluid most often blood-stained, sometimes clear and straw-coloured, sometimes organised; a varying number of petechial haemorrhages in the epicardium and perhaps the endocardium particularly of the left ventricle; some congestion of the lungs, small bowel, and kidneys which might in addition exhibit varying degrees of pulpiness. Those who had been concerned with the investigation of mortalities among ewes in spring and summer would have been impressed by the large number of such losses which fitted into that category. It was not surprising, therefore, that shepherds, concerned particularly with sudden deaths in their flocks, had no other thought very often but that enterotoxaemia under any of its popular names was responsible. The authors stated that in 9 out of 10 animals examined immediately after death " except for the presence of gas in the intestine—very few abnormalities could be found, although a number had a large excess of clear fluid in the pericardial sac " and " one animal examined 12 hours after death showed the typical pulpy kidney lesion." It was not quite clear whether the reference was to 10 lambs or 10 ewes, but the lesions were so meagre as to offer little concrete specific evidence which would eliminate all but enterotoxaemia. Since one seldom had the opportunity of examining a carcase immediately after death, it would be of interest if the authors could offer any explanation for what at first sight would appear to be a difference—more than merely a difference in degree—between the *post-mortem* lesions as seen in field cases compared with artificially induced cases, and state whether it was necessary to take those differences as being serious for purposes of diagnosis. It would appear that the veterinary surgeon in the field might find himself in some difficulty in making up his mind as to the cause of death. What had the laboratory to offer as aids to diagnosis?

On the grounds that death was due to a specific bacterium found in the bowel, did the demonstration of its presence there in any way help in diagnosis? " No," said the evidence presented by the authors, for up to 46 per cent. of normal sheep harboured that organism in their bowels. The actual cause of death, they pointed out, was the epsilon toxin produced by the rapid proliferation of *Cl. welchii* type D. Could the mere demonstration of that in the bowel aid diagnosis? Again, the answer would appear to be in the negative, for the authors presented evidence that concentrations as high as 8,000 M.L.D. per gramme could be tolerated. The evidence would suggest, further, that if there should be any natural antibody present, the amount of toxin tolerated might be even greater. Again, experience suggested that even in cases of the disease, no toxin could be demonstrated at times. In view of that, and the close similarity of the disease in many of its aspects to metabolic disorders, it would be of interest if the authors could state whether they made a chemical analysis of the blood of their experimental sheep and, if so, what their results were. If it were not undertaken at the time, he suggested that such information would be most valuable if an opportunity presented itself at a future date.

One of the characteristic effects that epsilon toxin had on absorption was the production of a hyper-glycaemia. That was reflected by an increase of sugar in the urine. The detection of sugar in the urine must be regarded, therefore, as very valuable additional evidence of enterotoxaemia. However, experience showed that little or no urine could be collected at *post-mortem* examination of ewes. The position was quite reversed in the case of the lamb where the bladder was usually distended. Had the authors noted that difficulty?

As a further aid to diagnosis he desired to mention the examination of smears made from intestinal contents. That was a method used by Bennetts in Western Australia in his original work on that disease. It consisted of taking a standard loopful (one-eighth of an inch) of ilium contents at a point 3 yards forward of the ileo-caecal valve. That was spread over an area of one inch square on a microscope slide, dried, fixed in air, and stained by Gram's method. The slide was examined under the microscope and the number of Gram-positive, capsulated, Welchii-like organisms present in each field were counted. After much trial and error cases had been accepted as being suggestive of enterotoxaemia if 5 out of 10 such fields each contained at least 25 organisms to the complete or almost complete exclusion of all else. The results obtained after a series of about 200 consecutive *post-mortem* examinations encouraged the introduction of the smear examination as a further aid in routine diagnosis. Since that date it had been noticeable that the incidence of cases diagnosed as being enterotoxaemia, allowing for a normal annual variation, had fallen. How far that was a real reduction due to that method of diagnosis he was not prepared to say, and he

offered the following figures for what they were worth. In 1953-4 enterotoxaemia represented 29 per cent. of 530 *post-mortem* examinations; in 1954-5, 24.8 per cent. of 613 examinations, and in 1955-6 only 13.5 per cent. of 430 examinations. He understood the authors had experience of that method of diagnosis and it would be interesting to have their comments on its value as an additional aid.

He repeated that before one could estimate the incidence of a disease and before it could be adequately prevented, it must be capable of exact diagnosis. He had endeavoured to point out the difficulties entailed in diagnosis in the light of the information given in the paper, and would ask the authors how, in the light of their experience, they would set about making a diagnosis of enterotoxaemia in a ewe found dead 12 hours previously. He had also indicated that the apparently high incidence of the disease might be explained on the grounds of faulty diagnosis and inappropriate use by lay people of perfectly efficient biological products.

The authors concluded that "losses due to enterotoxaemia could be more adequately controlled by avoiding sudden changes of diet and preventing sheep overeating" as well as adequate vaccination. It was not always an easy matter to avoid those sudden changes at pasture since many might be precipitated by a mere change of weather, and he suggested for the purposes of discussion that the proper use of the available biological products following a correct diagnosis was even more essential if losses from enterotoxaemia were to be reduced.

He was grateful to the authors for their valuable paper despite the difficulties to which their information appeared to give rise. They had, in fact, restored his faith that there was such an entity as enterotoxaemia in ewes—a matter that at one stage he was beginning to doubt.

The General Discussion

Mr. A. Thomson (Beckenham) said he wished to thank Dr. Bullen and his colleague Mrs. Batty for a very excellent paper. The work which had been undertaken had filled a need, and as Mr. Rowlands had said it reaffirmed our faith that pulpy-kidney disease was a real entity.

He felt that whilst management might play a part in the prevention of pulpy kidney disease, present-day intensive methods of sheep rearing placed a great strain on the digestive system of the sheep, and predisposed it to the activities of *Cl. welchii* type D. He thought that farmers would be reluctant to alter their methods of husbandry, and could see no alternative to adequate vaccine and serum therapy. Mr. Thomson agreed with Mr. Rowlands that where the application of pulpy kidney prophylactics was left in the hands of the farmer, they could be misused, and poor protection could lead to a loss of faith in these preparations.

He wished to correct an impression that Mr. Rowlands might have given in his opening remarks in relation to the Therapeutic Substances Order, 1952. This Order controlled only the purity and sterility of biological preparations—it did not lay down standards for potency. There could still be on the market some biological products of low potency and he felt that the sooner this aspect of the matter was reviewed the better.

Mr. Thomson said that he personally had not experienced a breakdown in sheep which had been adequately vaccinated with a potent vaccine, and he wondered whether it might be helpful, in making a differential diagnosis, to have a few blood samples taken from the flock and examined for the presence of circulating antitoxin. Dr. Bullen had pointed out in his paper that if the circulating level of specific antitoxin were above a certain level, it was extremely difficult to infect the sheep by his methods. This he felt sure would also apply under natural conditions, and in flocks where losses continued in spite of vaccination it would be most helpful if in a small cross-section of the flock it could be confirmed that the antibody levels were adequate.

Mr. H. E. Harbour (Berkhamsted): "Dr. Bullen has remarked on the effect of a slowing-down of the rate of movement of intestinal contents in producing conditions favourable to the development of enterotoxaemia. It is a common experience to see outbreaks of pulpy-kidney disease immediately following dosing with phenothiazine or other anthelmintics, or even on occasion following the gathering of sheep for other purposes, *e.g.* dipping. Does Dr. Bullen feel there is a real connexion between these circumstances and the development of enterotoxaemia or would the outbreaks be regarded simply as coincidences?"

The Replies

Mrs. I. Batty, in reply, wished first to thank the B.V.A. for inviting her to take part in that year's Congress. She had been very pleased to meet Mr. Rowlands from whom specimens had been received from time to time over a number of years.

As to whether it was known if the vaccines in use were efficient or not, she agreed with Mr. Rowland's suggestion that vaccines and sera were sometimes used at times which were not the most advantageous. If a sheep were dying, it was obviously too late to start vaccinating it; on the other hand if a sheep were given a dose of serum, the protection could not be expected to last over a long period of time. Errors of this kind might sometimes occur, especially when shepherds had to rely on their own discretion. Amongst laymen confusion between the uses of sera and those of vaccines did sometimes occur.

Mrs. Batty said they had not found it possible to produce experimental enterotoxaemia in sheep which had reasonable levels of circulating epsilon antitoxin; it might therefore be useful if in some supposed outbreaks of enterotoxaemia the level of epsilon antitoxin in the flock could be measured. This might help to sort out some of the cases diagnosed as enterotoxaemia merely on the evidence of finding *Cl. welchii* type D organisms in the gut.

From their work on both mice and sheep it seemed that not only was the concentration of epsilon toxin important, but also the length of time that this concentration was allowed to remain in the gut.

Dr. Bullen also, in reply, said that on the question of diagnosis one had to take a great many things into consideration as in other diseases. It seemed reasonable to suppose that many of the signs observed in cases of enterotoxaemia developed *post mortem*, and that was one of the things suggested by Bennetts in his original work.

So far as criteria were concerned, the idea of looking at a smear in the case of enterotoxaemia was a good one.

With regard to the question of the toxin, it was of course essential to make sure that one was dealing with epsilon toxin. If it were present then the sheep could have died from enterotoxaemia.

The question of levels should be investigated further. There seemed to be some circumstance connected with the death of the sheep which allowed toxin to disappear from the gut. The toxin was stable in intestinal contents removed from the animal and kept at $+4^{\circ}$ C. Whether it was absorbed onto dying tissue was not known; but there was good evidence that there was rapid decline in toxin levels immediately death had occurred. That made it difficult to assess the level there was in the sheep before the symptoms began to appear.

Professor Glover was one of the first people to observe the appearance of sugar in urine after the animal's death from enterotoxaemia, and that observation tied up well with the work of Gordon and Taylor. If one could obtain a sample of urine and look for sugar by a simple test, a positive result was a good indication of enterotoxaemia. He agreed that in old sheep it was difficult to get urine, but even one drop could give a strong reaction, and might be of considerable value.

The *post-mortem* appearance was in fact of considerable value. The appearance of the thick material which developed in the ileum was a very common and persistent finding.

It was interesting to hear reviewed once again the historical background, and a debt of gratitude was owed to Dr. Wilsdon for originally sorting out the *Cl. welchii* strains. As to the *p*H in the intestine, the *p*H of the ileum was about 7.5 and it did not alter very much whatever occurred in the rumen or duodenum.

XUM

He agreed on the difficulties of producing animals under intense conditions. However, if sufficiently high concentrations of antibody were present in the blood, the sheep were completely immune to enterotoxaemia. Sudden changes of diet and overeating should also be avoided. It was impossible to reproduce enterotoxaemia experimentally if the diet were allowed to change from hay to wheat sufficiently slowly.

Convulsive and Allied Syndromes in New-born Foals

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Introduction

DURING an address to the annual meeting of the Lincolnshire Division of the N.V.M.A. in 1930 Reynolds (*loc. cit.*) described and discussed a "nervous affection" in new-born foals. These, he said, made a peculiar noise like the yapping of dogs and because of this, stud grooms in the Newmarket district often referred to them as "barkers." There were a few cases every year, symptoms appeared shortly after birth and frequently soon after the first time the foal had sucked. It went down and was unable to regain its feet, there were clonic spasms, struggling, galloping movements and apparent blindness. The prognosis was considered unfavourable, although one case had recovered and eventually won good races whilst another had subsequently done well after having been "inclined to wander" for several days. The condition appeared to be confined to Thoroughbreds and sometimes, though not always, it occurred concurrently with fractured ribs and bruising of the heart. Infection did not seem a likely cause and no lesions were recognised at *post-mortem* examination. Reynolds had wondered whether the nervous symptoms might not be caused by some deficiency in the circulation of the brain, resulting from a bruised heart but, all things considered, he took the view that the malady was purely nervous in origin although he was at a loss to give it a name and there were many uncertain factors involved.

This seems to be the first reference in the literature to a clinical syndrome which is now a well-recognised entity in most of the larger Thoroughbred practices in England and Ireland. Fraser (1939), Leader (1952) and Cosgrove (1955) have all discussed the condition in papers dealing with foal diseases without being able to add anything of significance to Reynolds's original report. It is noteworthy that there is nothing in the literature from other Thoroughbred-breeding countries concerning a similar condition. Meissner and Koser (1935) do not list it in their comprehensive treatise on diseases of foals in Germany. The lectures delivered from 1951 to 1954 at each of four annual stud managers' courses in Kentucky have been published. All the foal diseases which occur commonly in that locality are described briefly, without any mention of a syndrome in which "barking" and convulsions are predominant signs. Grootenhuis (1956) does not deal with a similar disease in his comprehensive survey of breeding problems amongst heavy horses in Holland and, in a personal communication, expressed the opinion that no such condition occurs in his country. One of us has had extensive experience of Thoroughbred-breeding practice in Australia where foaling methods differ markedly from the common procedures in operation at British and Irish studs. Like Bain (1954 and 1956), he has neither seen nor heard of a "barker" there. We shall return to these points later.

Obstetrical Procedures at Studs

In almost all the larger Thoroughbred studs in the British Isles managers aim at having mares foal indoors under supervision in rather spacious and well-appointed foaling boxes. Attendants are stationed in an adjacent room and in the intervening wall there is generally a sliding panel through which the mare may be observed unobtrusively. Whatever the hour, mares which are near term or which are otherwise thought close to foaling are kept under careful observation in the box. When signs of restlessness, increasing uneasiness and sweating appear, a constant watch is maintained. Quite early in labour, generally soon after "the breaking of the water," the groom ascertains the type of presentation. If it is normal he waits quietly nearby for the mare to become recumbent (as the great majority do) during her labour pains and prior to her final expulsive efforts. A small minority of men do little or nothing more until the foal is clear of the vagina; the majority, however, practice some sort of "interference" with the otherwise normal course of parturition soon after the forelimbs and head are visible at the vulva. This assistance varies a good deal from stud to stud in accordance with individual traditions and with the particular beliefs of stud grooms. Help is rendered particularly when there appears to be any undue prolongation of the process of delivery, but mere habit is often the dominating influence. The least degree of aid is a holding and steadying of the limbs, more frequently traction is employed and it takes the form of a steady pull on the forelegs by one man. Occasionally the strength of two men is called into action and their efforts may or may not be in unison with those of the mother. The pull continues until the chest is clear of the vagina and often until one or both hind legs are delivered.

For one reason or another some nervous mares get up quickly at this point and in so doing, the umbilical cord is ruptured. A somewhat similar early rupture is precipitated by those grooms who drag the new-born around to the mother's head as soon as it is delivered. Apart from these cases, and irrespective of what assistance has been given before, almost everyone displays an urgent desire to attend to the

cord at the earliest possible moment. It is made readily accessible by peeling back the amnion and, with or without ligation, is artificially severed. Usually the amnion is then tied up in a large knot in order to shorten it and so prevent the mother from treading upon it.

After it has passed the lips of the vulva severance of the cord is usually accomplished within one minute, a time interval which is significantly shorter than under natural conditions. In a general study of parturition in the mare, Rossdale and Mahaffey (1957) have shown that these methods result in the newborn being deprived of a very substantial quantity of placental blood. Following early severance we have found that between 500 c.c. and 1,500 c.c. of blood can be collected from the maternal end of the cord. This is in striking contrast to the volume obtainable when it is allowed to remain intact until pulsation has ceased. Rarely more than 150 c.c. can be collected at that stage.

There are other respects in which an assisted foaling may differ significantly from one during which there is no human interference. The foetus is often made to assume rather unnatural postures during its passage through the birth canal and sometimes immoderate force is applied to it. Not infrequently there is a tendency to hustle the new-born and to get it to suck quickly irrespective of its general condition.

The possibility that procedures which deprive a foal of considerable placental blood (and which introduce a variety of other factors) may sometimes have an adverse effect upon its welfare cannot be dismissed lightly and has been engaging our attention for some time.

Incidence

From January to June each year between 1,000 and 1,250 Thoroughbred foals are born in the Newmarket area. Of these some 2 per cent. become "barkers," "dummies" or "wanderers"; clinical conditions which appear to be closely related. They seem to have been more consistently associated with some studs than with others but most have had experience of them during the past 30 years.

The foals concerned are of either sex, of varying weight, coat colour and general condition and there does not seem to be any association with post- or pre-maturity. Most cases occur after an easy and uneventful birth. The age, condition and past history of the mares are quite variable and they may be primiparous or multiparous. We know of a few cases of mares having several affected foals, sometimes in successive years at different studs. This might suggest an inherent susceptibility in some individuals but there is no evidence that hereditary factors are directly involved. Furthermore, the pedigrees of Thoroughbreds in most parts of the world contain the names of constantly recurring common ancestors from the grandparents backwards but the syndromes under investigation appear to have quite limited geographical distribution.

Neither we nor any of our friends and colleagues in practice have ever seen cases in non-Thoroughbreds which (by coincidence or otherwise) foal under quite different conditions, usually unattended in a field. We have no knowledge of similar syndromes occurring in other species.

General Clinical Description

We shall describe in general terms the symptoms exhibited by foals which become typical "barkers" soon after birth. Before they recover they pass through phases during which they are referred to as "dummies" and "wanderers." This is a common sequence but there are foals which begin as dummies, or as wanderers, just as there are convulsive foals which never make a barking noise.

Definite symptoms are usually apparent within a short time of birth, commonly after an hour or so, by which time many foals will have had their first milk. However, there are numerous cases on record where the first signs were seen in from 10 to 30 minutes and before the foal had sucked. There are also a few instances of the onset being delayed 12 or more hours, but never beyond 24.

Some premonitory signs

Stud grooms and attendants usually report that the foal appeared quite normal at birth. After minutes or hours it may be seen jerking its head up and down in a strange fashion, the legs moving aimlessly (though not violently) without any attempt to get up. A foal already on its feet may become unsteady, weak and suddenly recumbent, or it may wander around the box colliding forcibly with the walls. This preconvulsant stage is not always apparent, when it is, it occupies a period of only a few minutes.

The Barking and Convulsive Phase

After seeing a foal on its feet sucking normally (usually within one to two and a half hours) the studman may leave only to be recalled by the barking sound emitted by an animal in convulsions. Everyone describes this noise as "barking" although it reminds different people of different things—a dog (a yapping terrier) a fox or even a ewe; for some it is an eerie sound, others are reminded of a "mad" dog; late on a still night the veterinary surgeon might hear it 100 yards away, sometimes it is only audible across the yard; in any event it is capable of starting a neighbouring dog barking. We have not been able to satisfy ourselves as to the mechanism by which the noise is produced, nor indeed, whether it is upon inspiration or expiration but at times we have had the impression that it was emitted whilst the thoracic cage was in a momentarily "fixed" position.

In the early convulsive stage there are clonic spasms of the muscles of the head, neck, body and limbs. The foal may sit on its haunches with the forelegs stretched in front of it showing nystagmus and champing jaws. Sometimes it whinnies loudly once or twice. After an interval lasting a few or many minutes, a second and more violent phase of convulsions follows these early symptoms.

The foal collapses on its side and the whole body becomes involved in violent inco-ordinated motor convulsions.

These may resemble those of the excitement stage in chloroform anaesthesia, with galloping motions of

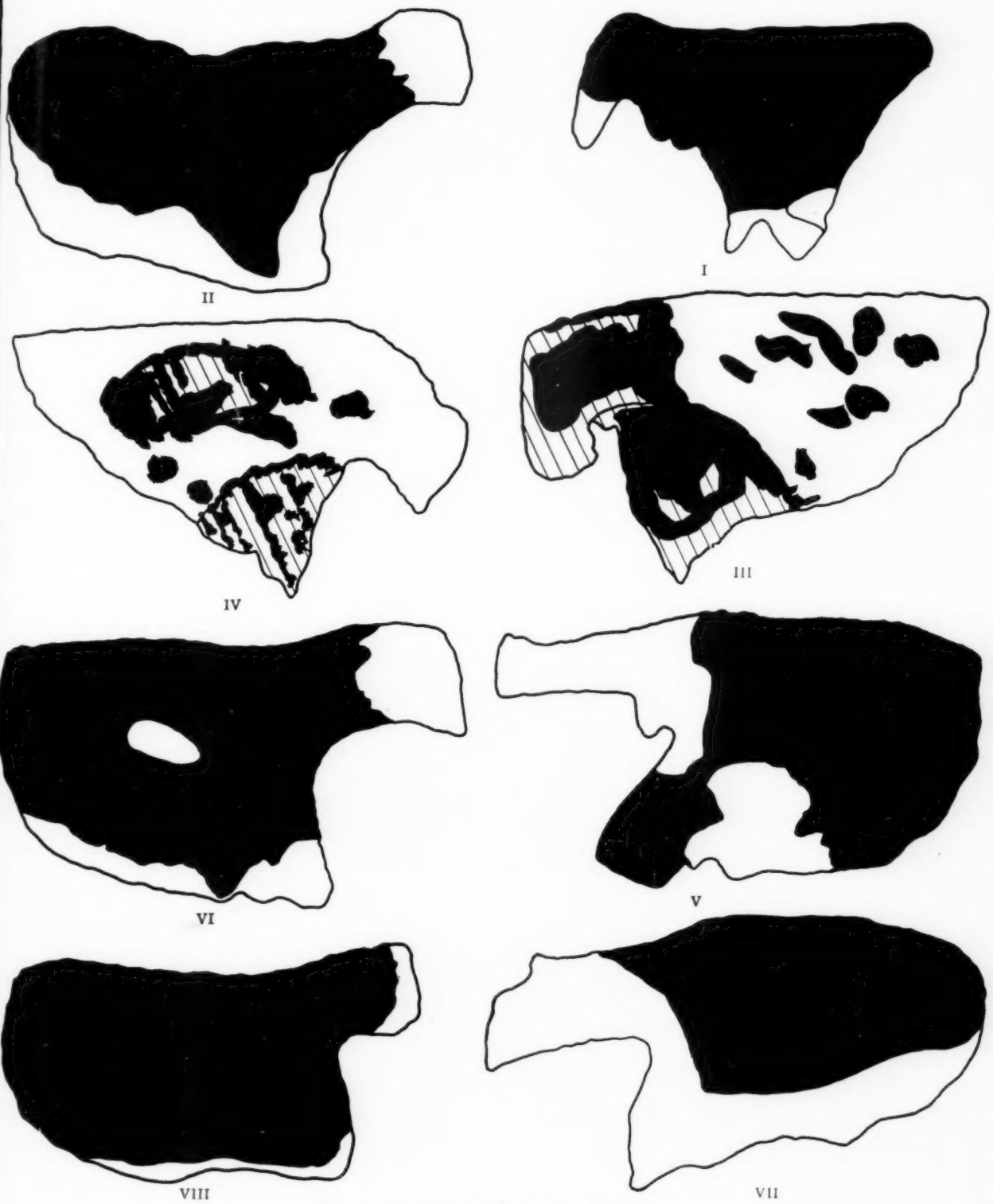

FIG. 1.—DIAGRAMS OF "BARKER" LUNGS.

Left		*Right*	*Left*		*Right*
II	Died at 18 hours old.	I	VI	Died at 36 hours old.	V
IV	Died at 6 hours old.	III	VIII	Died at 4 days old.	VII

Areas of abnormal lung shown in black.

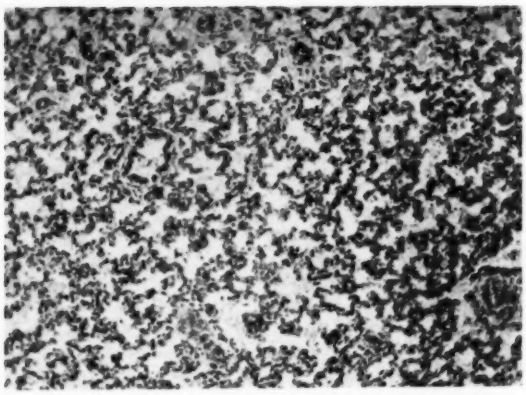

FIG. 2.—Appearance of normal full term foetal lung x 200.

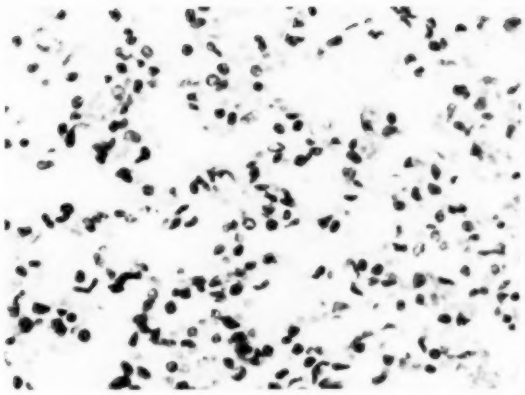

FIG. 3.—Appearance of normal full term foetal lung x 900.

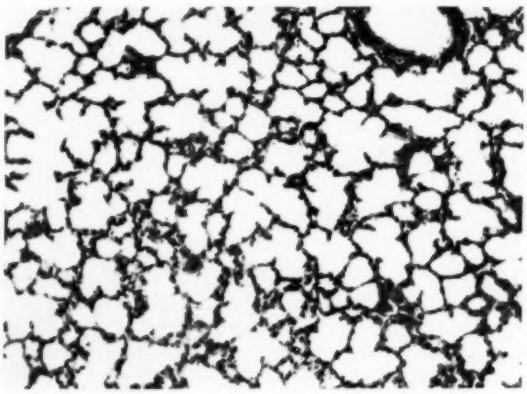

FIG. 4.—Appearance of normal lung 4 hours old x 200.

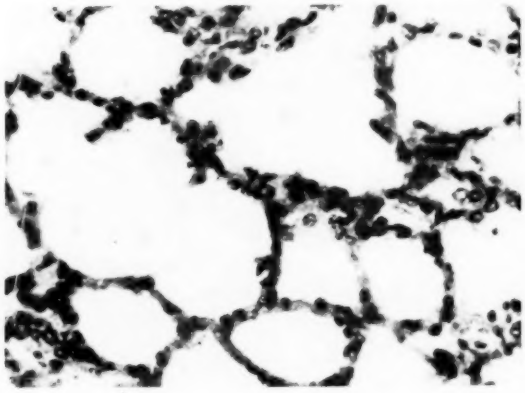

FIG. 5.—Appearance of normal lung 4 hours old x 900.

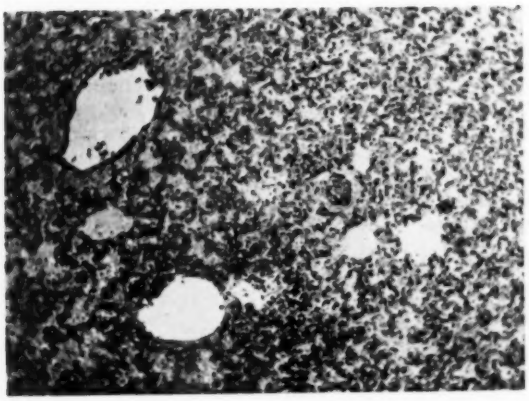

FIG. 6.—Appearance of barker lung 36 hours old x 200.

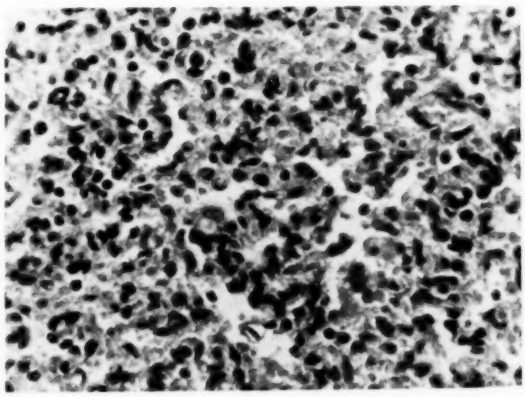

FIG. 7.—Appearance of barker lung 36 hours old x 900.

the limbs and powerful interrupted contractions of the muscles of the neck and back. Any form of restraint tends to accentuate these movements, but if it is not held down forcibly the foal throws itself about on the ground and as a consequence there is often severe bruising around the eyes and mouth.

The combined efforts of as many as three or four men are sometimes required to exercise the necessary restraint. There is often profuse body sweating and the rectal temperature rises several degrees above the normal. If barking is present it usually only persists during part of this convulsive phase.

The heart rate is greatly accelerated, at the height of the convulsions it reaches 200 or more per minute. The rate and depth of the respiratory movements vary with the intensity of the convulsions and at times they are greatly exaggerated. The nares are widely dilated. Auscultation of the lungs during this stage is made difficult by the violent movements of the foal. Loud harsh sounds can be heard over the entire lung areas and there are usually no detectable silent areas. Vibratory and sibilant sounds may be heard but their significance is not clear as they are not constant features. The visible mucous membranes are usually pale grey in colour. They do not show obvious evidence of cyanosis.

The pupil varies in size in different individuals, most often it is dilated and responds sluggishly to strong light. The media, disc, and retina of the eye appear normal for a new-born foal although in one case numerous red spots, probably petechiae, were observed on the retina. Meconium, often with flatus, may be passed during this stage.

The Stage of Coma or Semi-coma

The veterinary surgeon is always called early in the convulsive stage, commonly while "barking" still persists. Since it is obvious that the convulsions, in themselves, are dangerous and most exhausting, it has been common practice over the years to administer narcotising, tranquillising or anticonvulsant drugs such as chloral, the barbiturates and lately, mysoline*. All of these have varied a good deal in their ability to alleviate or control the seizures in any particular foal and in grave cases more or less continuous convulsions may go on for many hours. Some die during this period but the majority, whatever is done, ultimately pass into a state of coma or semi-coma. They lie on their sides with the eyes closed, head extended and the neck and back slightly arched.

A few lapse into deep unconsciousness from which they may never recover but many are easily aroused by a variety of sudden noises, a man's voice, a moving door or a sharp tap on the body (almost as though they were hyperaesthetic).

There are alternating periods of quietness and purposeless muscular activity during which the respiratory and heart rates vary considerably. Particularly in the earlier stages the respiration is quicker and deeper than normal and inspiration through the mouth, in a fashion suggestive of air hunger, is often observed. Mild convulsive movements occurring spontaneously, or as a result of external stimuli, cause both the respiratory and the heart rate to increase out of all proportion to the exertion involved. In just a few seconds the former might go from 30 to 60 and the latter from 90 to 160 per minute. Even during the quiet phases the dilatation of the nostrils and the corresponding action of the superficial muscles which control this process may be very pronounced. From time to time one may see a strong jugular pulse (at about 100 per minute), a sporadic paddling of the upper forelimb, brief galloping movements and what might be interpreted as primitive efforts to get up. Such a foal is quite unable to stand if attempts are made to get it on its feet and when the body is supported it is incapable of holding its head up properly. It cannot make use of its visual sense and neither its mother nor men seem to have any real meaning for it; in certain respects it is like a foetus, especially in that some of the essential extra-uterine reflexes are suppressed. During all this time the body temperature usually remains normal (ca. 100° F.), especially if accommodation is provided in a warm box, as is the habit in Newmarket, or if rugs are used. However, it may sometimes fall as low as 96° F. for a brief period and then the extremities are noticeably cold to the touch.

This stage lasts for hours or days, during which the foal must be fed by stomach tube. The coma may get deeper and deeper and eventually terminate fatally or, gradually, and almost imperceptibly, it may become lighter and the foal develops into a "dummy" or "wanderer."

Wanderers and Dummies

This phase invariably constitutes a stage in the progress towards complete recovery, but as we have mentioned earlier, a number of foals are dummies or wanderers from birth and never experience barking, convulsions or real coma, although a few which behave like marionettes or complete dullards seem on the verge of these symptoms. The behaviour and course of the disease in either instance is similar from now on.

Generally the postural reflexes are very nearly normal. The dummy or wanderer is able to stand, hold up its head and shake itself in typical equine fashion, none of which were possible earlier. It seldom lies down voluntarily but if placed on the ground may go to sleep and remain in the same position until disturbed, when it can get up unaided. The normal relationship with the mother is still in abeyance; it is indifferent towards her and she may be taken from the box without causing the least alarm. None of the usual reactions of a normal foal towards the presence of man is evident, there is no fear, some learn to come when called and may nuzzle into one's legs. There is still apparent blindness or the foal is oblivious to objects with which it is not actually in contact. It appears to live in a world of sound and touch which it scarcely comprehends and may wander slowly around the box with the ears pricked and rotating as though to catch the slightest noise. At first there is little deliberate response to what is heard but later an attachment to sounds and procedures associated with feeding develops. The sucking reflex may remain absent for a long time. A

* I.C.I. Primidone B.P.

wanderer merely bites on or chews at the teat on a bottle and to provide adquate nourishment it is essential to feed often *via* the stomach tube.

Although a lot of time may be spent wandering and colliding (or almost colliding) gently against the wall, many occupy themselves standing about idly chewing straw, which is picked out of the bedding but not swallowed. Handling the body is rarely resented but some become agitated when the head is restrained to pass the stomach tube; there is response to painful stimuli such as needle pricks.

The rectal temperature is normal, the heart rate regular in rhythm at 80 to 120 per minute and the respiratory rate varies with bodily activity in a fairly normal manner.

The thoracic movements are shallow and regular, auscultation reveals apparently normal sounds in both lungs although the intensity is variable even in neighbouring areas.

This stage, which lasts on the average three or four days, may drag on for ten days. The normal, hitherto absent reflexes return gradually, the foal may suck on the finger before swallowing milk from a bucket or bottle. Finally it can be persuaded to suck the mare and after this the normal foal-mother affinity and relationships are established in nearly all cases. Blindness disappears and apart from a somewhat dehydrated appearance and some healing bed sores, the general appearance is rather good and the foal well on the way to recovery.

In those that recover there are no apparent residual effects whatsoever.

Prognosis

The prognosis depends to a large extent upon the duration and severity of the convulsions and perhaps more than usually in veterinary practice, upon the management of the case.

Some very early deaths occur in foals afflicted with continuous, violent, uncontrollable seizures and one must be very guarded with the prognosis throughout the phase of convulsions and coma. A mortality rate of 50 per cent. should not be considered unusual and it seems to be closely associated with the development of extensive pathological changes in both lungs.

Once the stage is reached at which the foal is able to stand and walk unaided, the outlook is very favourable provided careful nursing is practised until it is sucking the mother, and unless convulsions reappear, which is quite rare.

The prognosis is similarly good for those wanderers and dummies which have not experienced barking, convulsions or coma.

Treatment

Since there is no specific, dramatic cure at any stage of the disease, treatment is aimed at quietening and restraining the foal so that it does not exhaust or injure itself. Coincidental measures to prevent inanition and dehydration are required. Good nursing (which involves the use of valuable labour at a particularly busy time) is the primary consideration and it must not be relaxed throughout the entire course of the condition until the foal is feeding itself from the mother.

As Leader (1952) observed, there is a high percentage of spontaneous recoveries when the "convulsions do not last too long and are not too severe" and cases have ended successfully when the foal has merely been "held down until the convulsions passed" and subsequently fed artificially until it learnt to suck.

Naturally suitable drugs to control the convulsions have always been sought. It has never been possible to give any one of these a stringent trial. Chloral *per rectum* did not seem adequate; barbiturates, as used, were not very satisfactory and under the prevailing conditions intravenous injections were sometimes followed by deep coma or even immediate death. For several years mysoline has been the drug of choice and, deservedly or not, is now part of the routine treatment in Newmarket. The usual initial dose is 2 to 3 g. *via* a stomach tube followed by a further 1 to 2 g. if convulsions do not subside within half to one hour. These doses are sometimes varied a little, or combined with chlorpromazine hydrochloride*, and they are repeated more or less as the veterinary surgeon thinks fit, usually at 12- to 24-hour intervals. We have made some preliminary investigations into the activity of mysoline in new-born foals and as a result of these we favour the use of rather larger quantities; even 6 to 8 g. within the first hour does not constitute over-dosage; subsequent doses depend upon the degree of control achieved.

At the height of the convulsions the foal must be physically restrained, one man is needed at the head and one and often more at the legs and body. If the seizures are mild, one man sitting with the head across his lap and holding a forelimb is sufficient. Loss of body heat is prevented by having a warm box or by the use of rugs. Attention should be given to preventing or minimising head and eye injuries and bed sores on the thighs, since these can develop very rapidly. Quietness is of great importance and quite minor noise may lead to varying degrees of useless muscular effort.

Food must be provided in as nearly normal a manner as possible. A normal foal in the first few days will suck from the mother at least every hour, and this would be the ideal interval for the barker or wanderer but it is almost always impracticable. The best that can usually be managed is to give ½ to ¾ pint of the mother's milk *via* the stomach tube every three or four hours. It ought not to be administered too quickly since hasty administration may lead to flatulence, pain and colic; the funnel ought to be just a little above head level as the milk is poured in. It is good procedure to wash the tube through with a little clean water before withdrawing it.

Appropriate antibiotic treatment, usually at least with penicillin, is commenced at the beginning and given until the foal is standing permanently. Antibiotic ointment is used on the swollen eyelids and it is often necessary to stitch back the lower lid temporarily to prevent corneal abrasions from the temporary entropion which follows the swellings.

Bed sores require the usual attention.

* Largactil. May & Baker, Dagenham.

When the foal is able to stand and walk it is fed from the bottle, or a bowl, which it learns to suck, and finally the attendants, after varying degrees of difficulty, teach it to feed from the mother. In exceptional cases a foal may have to be reared entirely by hand and never feeds from its mother.

Biochemistry

Although the clinical symptoms during the convulsive phase of the syndrome are not unlike some manifestations of severe metabolic disturbances it has not been possible to demonstrate consistent and significant differences in the serum level of calcium, magnesium, phosphorus, sodium or potassium from those found in a series of apparently normal new-born foals.

The results of analyses from these and from six acute cases are set out in Table I. The number of barkers is rather small but in each instance the blood was obtained when symptoms were very marked and when one might expect a mineral factor of primary aetiological significance to be readily demonstrable.

We hope to have from individual new-born foals, normal and otherwise, a series of biochemical estimations on cord blood, and jugular blood at short intervals up to about 48 hours, but so far we have not been able to undertake this task.

We have had serum protein estimations made on the cord blood of nine foals which subsequently remained perfectly healthy: the mean values in grammes per 100 ml. were: total protein, 3.8; albumin, 2.7; globulins, 1.1; A/G ratio 2.4.

In three barkers which recovered the values for serum obtained from the jugular vein during the convulsive phase were:—

(A) total 4.1, albumin 3.1, globulins 1.0, A:G 3.1
(B) ,, 5.0, ,, 2.0, ,, 3.0, ,, 0.66
(C) ,, 3.5, ,, 2.2, ,, 1.3, ,, 1.7

Haematology

The haematology of six acute cases has been compared with the blood picture of 17 apparently normal new-born foals. Nothing of significance was revealed but, as with the biochemistry, we should like to know whether there is any difference in the early haematology of foals which have not been deprived of placental blood, and so are what one might call "naturally normal," and those which are normal in terms of Thoroughbred obstetrical practice, where early cord cutting and consequent blood deprivation is the rule.

The important red cell figures are set out in Table II.

With the white cells there has been no difference in count or morphology between "barkers" and "non-barkers."

Bacteriology

The general features of the disease do not suggest a bacterial or viral aetiology. Histologically there are no constant microscopic changes in any of the organs resembling those seen in infective processes. Cultures have been made from a variety of viscera in a number of cases and the only growth which was ever obtained came from the lungs. In two cases a strain of *Bacterium coli* grew in abundance but no doubt this was a secondary invasion since similar organisms are common in the lungs of foals dying from ailments

TABLE I

Foal	Serum Calcium mg. per cent. Method : Clark and Collip (1925)	Serum Magnesium mg. per cent. Method : Oakmoto and Thomas (1954)	Serum Inorganic Phosphorus mg. per cent. Method : Gomorri (1952)	Serum Sodium mg. per cent. Method : Flame Photometer	Serum Potassium mg. per cent. Method : Flame Photometer
Average of 18 normal new-borns ...	14·0 ± 0·3 S.D. 1·2				
Average of 20 normal new-borns ...		1·8 ± 0·14 S.D. 0·58			
Average of 9 normal new-borns ...			4·9 ± 0·5 S.D. 1·5		
Average of 18 normal new-borns ...				317 ± 15 S.D. 18;8	
Average of 15 normal new-borns ...					23·1 ± 1·3 S.D. 5·0
"Pre." Barker Died.	14·6	2·45			
E. V. 1. Barker. Recovered ...	12·5	1·85		325	11·0
Madame. Barker. Died					
8 Hours *Ante-mortem*				325	20·2
3 Hours *Ante-mortem*	12·9	1·2		315	32·5
N.F. 13. Barker. Recovered ...	12·4	1·6		330	20·0
E.V. 2. Barker. Recovered ...	11·5	1·85	4·0	320	16·5
P R. Barker. Recovered	11·6	1·5	3·9	300	18·0

TABLE II

	R.B.C. × 10^6	Haemoglobin grs./100 ml.	P.C.V. per cent.	M.C.V.
17 normal new-born foals ... ... Cord Blood	Mean 10 ± 0·39 S.D. 1·55 Range 8 to 14	Mean 15 ± 0·36 S.D. 1·45 Range 11 to 17	Mean 43 ± 1·2 S.D. 4·8 Range 37 to 56	Mean 41 ± 0·4 S.D. 1·6 Range 32 to 47
Pre. Barker. Died	13·9	19·4	54·6	39
E.V. 1. Barker. Lived	11·9	18·0	49	41
Madame. Barker. Died				
(*a*) 90 minutes *post partum* ...	10·85	16·9	47·5	44
(*b*) 8 hours	10·67	16·7	45	42
(*c*) 3 hours *ante-mortem*	12·4	17·9	50	41
N.F. 13. Barker. Lived	9·65	14·5	38·5	40
E.V. 2. Barker. Lived	11·35	15·5	44	39
P.R. Barker				
At 3 hours	10·1	16·6	44·5	43·9
At 36 hours. Lived	9·9	16·3	42·0	42·4

which do not resemble barking. Coliforms commonly accompany *Bact. viscosum equi* in early neonatal infections and we know them to populate the nasal passages very soon after birth.

We have never seen the latter organism associated with the syndrome we have described but it is fairly common in England and is regularly recovered from "sleepy" foals. On one occasion we found it to be responsible for a syndrome which clinically one of us thought possibly an atypical barker since there was noisy, rapid breathing and coma and several men were required to restrain it. At *post-mortem* we found lobular necrotic pneumonia and renal cortical abscesses from which *Bact. viscosum equi* was recovered.

In America, Sagar (1956) informed us foals which had symptoms resembling wanderers almost always proved to be cases of *Bact. viscosum equi* infection.

Post-mortem Appearances

Swollen eyelids and circular abrasions around the eyes and hips (less frequently on other parts of the body) resulting from convulsive movements whilst the foal is recumbent are commonly present.

Within the body cavities gross macroscopic lesions have been confined to the lungs. In five out of six cases which died in from 24 hours to four days they were of similar nature and distribution and in each instance both lungs appeared extensively consolidated. When the thorax was first opened they were generally decidedly blue, rather resembling non-aerated equine foetal lungs. Like the latter they rapidly assumed a red colour upon exposure to air and then they had the macroscopic appearances of lungs which are the subject of extensive red hepatisation. The only portions with a normal appearance have been confined to the anterior portion of the apical lobes, to areas in the lower portions adjacent to the cardiac notch and to quite small areas along the basal border of the main lobe (or body) of the lung.

These striking abnormalities have never been mentioned by clinicians, who have generally believed that there were no constant lesions in their *post-mortems*. We, on the contrary, have been most impressed by the extent of the changes and the rapidity with which they develop; we feel sure they are the direct cause of most of the deaths and are probably the main hazard in the disease.

Because of the consistency with which we met them, even in foals dying within 36 hours, we thought at first that they might be the primary lesion and we wondered at the possibility of there being some congenital alteration in pulmonary structure, or derangement of physiological processes controlling expansion at birth, and whether the convulsions stemmed from an anoxia consequent upon pathological or subfunctional lungs. However, the occurrence of a very acute case which exhibited barking and convulsions within 30 minutes of birth and died five and a half hours later, led us to view the matter rather differently. Although there was a considerable degree of atelectasis in both lungs in this instance, the lesions were appreciably less extensive than in our other cases which died later.

We have been able to examine many foetal, stillborn and new-born lungs during the past few years. In congenitally deformed foals, destroyed at or soon after birth, we have observed that very little respiratory effort is necessary, normally, to convert bluish, non-expanded foetal lungs into the characteristic postnatal organs. In a foal with a congenitally open abdominal floor the very delicate pastel pink colour and feathery texture was seen to have developed uniformly in both lungs within six minutes; in another, with deformed limbs and destroyed during parturition, a dozen or so gasps had seemed sufficient to produce normal expansion. Further, it is an easy matter to inflate the lungs of a full-term, stillborn foal artificially and they can be made to assume an aerated appearance very quickly.

Pieces of equine foetal lung examined as far back as the eighth month (or earlier) often float in fixative or water; the same applies to the full-term stillborn and it is invariably so in the new-born which has not been the subject of definite pathological processes.

Great areas of consolidated "barker" lungs sink rapidly and completely in fluid and the reason for this behaviour by the different lungs is readily appreciated when the histological features are studied; there we shall see that "barker" lungs have little microscopic resemblance to foetal lungs.

We are uncertain about the exact time and mode of development of the lung changes. Some clinicians believe that there is no evidence of inadequate pulmonary function during the convulsive phase. We have found it very difficult to assess the significance of the sounds heard with the stetnoscope in a foal which is quite violent; in these cases, and indeed in the older horse, we have found it a formidable task to decide whether air is passing beyond the small bronchioles and alveolar ducts*.

Quite tentatively we assume the lung lesions to result largely from the violent convulsive activity, with its rapid respiratory rate and presumably grossly excessive ventilation, although in some way other factors would certainly seem to be involved because the whole syndrome leads to a pathological state which mere increased respiration and recumbency from other causes seems incapable of producing. We had a case of *Bact. viscosum equi* infection in a new-born foal. For nearly 24 hours the respiratory rate was about 70 with obvious distress. It was recumbent the whole time and had to be held. At *post-mortem* examination we could easily distinguish the lungs from the barkers we have seen. The extent of the visibly abnormal lung tissue was very much less, superficially the differences were much as might be seen in a case of catarrhal compared with one of croupous pneumonia. At subsequent histological examination there were many small abscesses and no evidence of the extensive collapse characteristic of the barker.

Because we felt that a study of the circulation might shed light upon the syndrome we have examined the ductus arteriosus and foramen ovale in foetuses and foals up to several months of age which have died from various causes.

The structure and closure of the foramen ovale in normal foals have been described by Franklin *et al.* (1942) and by Ottaway (1944) and we have nothing significant to add to these descriptions. As in any normal foal of a similar age it has been anatomically patent in all the barkers we have examined *post-mortem*.

A cross-section of the ductus arteriosus in a full-term stillborn foal reveals a very patent vessel, some 30 mm. in circumference, which is so orientated in relation to the pulmonary artery and its two branches as to give the impression that the direct flow of blood is from the right ventricle to the aorta. Shortly after birth there is an obvious shift in direction of the ductus and the angle between it and the branches of the pulmonary artery increases from about 50° to 120° and coincidently a decided kinking effect is produced.

Although this change in the relative position of the vessels appears an important factor in re-routing blood just after birth, Born *et al.* (1956) do not believe it plays any part in the closure of the vessel. They believe, as Barcroft (1946) had originally suggested, that the main stimulus to constriction is the increased oxygen tension of the blood following the onset of pulmonary respiration.

By the end of the first 24 hours of extra-uterine life there is marked internal puckering, visible when the ductus is cut across, and the circumference becomes rather difficult to measure but it contracts to something of the order of 6 mm. (sufficient to admit a stout Pasteur pipette). Thereafter the lumen appears to become obliterated within a few days, although it may remain probe patent for several months.

In those barkers which we have examined *post-mortem* the ductus has been more patent than we expect to find in the normal foal of the same age. The circumference has always exceeded 22 mm. (even at four days) but we do not know the relative amounts of blood flowing through it and the two branches of the pulmonary artery nor do we know the direction of flow in the ductus, or the significance, if any, of it being apparently much more patent than in the normal foal; although it would not, of course, be a primary aetiological factor, presumably it could be a reflexion of a degree of anoxia. Dawes *et al.* (1955) have shown that a large quantity of blood passes through the ductus from the aorta to the lungs in new-born lambs and they postulate that this might be of physiological importance in a period when the lungs may not be functioning efficiently. However, this flow of blood can and does occur even with a constricted ductus. Over the position of the vessel in the new-born foal, we have often heard a murmur which probably has the same origin as that heard by Dawes *et al.* (1955) in the lamb, but we have not detected any quantitative difference between barkers and healthy foals. In a 15-day-old wanderer which had been an acute convulsive new-born and which died with extensive catarrhal pneumonia, the ductus resembled that of a normal foal of similar age and certainly appeared functionally inoperative.

Reynolds (1930) observed barking and evidence of damage from chest compression concurrently on several occasions but because the lesions were not consistently present he dismissed the possibility that they were of aetiological significance. Our own series of barkers happen to have been free of obvious thoracic damage but we frequently see broken ribs, bruising and evidence of compression in foals which do not resemble barkers either clinically or at *post-mortem* examination.

No macroscopic lesions have been seen in any organ in the abdominal cavity; the stomach has generally contained an excessive amount of air which has been gulped in by the mouth. It is possible that this is a minor source of oxygen.

* As an example of this we had very experienced clinicians examine a two-year-old with a persistently increased respiratory rate (45 per minute and dilatation of the nostrils). Each agreed that there were no apparent lung lesions, yet it was difficult to find, at histological examination, any normal lung tissue beyond the small bronchioles. These lungs were extensively affected with tuberculosis.

XUM

There have been no gross lesions of any kind within the cranial cavity of any of our cases. The meninges and cerebral blood vessels have never been congested and the brain itself has always appeared quite normal.

The weight and superficial appearance of the placentae of barkers have not differed from those of the normal foals we have examined but recently we have commenced a more detailed study of the membranes and umbilical cord in foals generally.

Histology

Microscopic examination of the lungs, liver, spleen, kidneys and adrenals and preliminary examination of brain tissue have been made. Furtner studies of the nervous tissue are in progress.

Until recently the lung changes have commanded most of our attention and we have generally taken sections from 10 or 12 areas in each and recorded the appearances in them. We found it necessary to compare these with normal foetal and new-born lungs; for this purpose we are fortunate in possessing ample material in the nature of a fairly representative series of foetal lungs from six weeks to term and from foalhood to an advanced age. Many were taken from twin foetuses which are frequently aborted at various stages. One twin usually appears to have been dead *in utero* for some time but the other is generally in an excellent state of preservation, it appears to have died shortly before the actual abortion and makes good "normal" histological material. We have also a considerable amount of tissue from foals the subject of dystocia (which died during delivery), from full-term still-borns of unknown but non-bacterial origin, and from various monstrosities and defective animals destroyed at various times after birth.

From about eight months the basic alveolar patterns in the lobules of the foetal lung are quite obvious and bear a distinct superficial resemblance to full-term and older lungs but individual alveoli are much more regular in shape and size and the capillaries are lined by, or in close proximity to, an "initial" epithelium of a characteristic type. The individual cells are cuboidal, with very sharply defined edges and clear cytoplasm. There is a large dark staining spherical nucleus, which occupies the greater part of the cell and contains many chromatin balls of variable size but no distinct nucleolus.

The alveoli near term are in no sense atelectatic or collapsed and the regularity in their shape and size suggests a fluid environment, although usually only 2 or 3 c.c. can be recovered from each lung after cutting along the bronchi and exerting pressure. Following the preparation of sections by ordinary histological techniques very little fluid is demonstrable in the great majority of foetal lungs, what there is being represented by fine, thread-like eosinophilic material, which is merely a reflection of the protein content of the fluid present. Structures resembling the vernix squames from skin, which are commonly present in human foetal lungs, are found irregularly dispersed throughout equine foetal and new-born lungs for days after birth. They are never very plentiful and are often to be found amongst the cellular components of the lung rather than lying free in the alveoli. Very occasionally fine fragments of golden yellow pigment, which appears to have a faecal origin, are scattered throughout the organ. The interlobular septa are very conspicuous in the foetal lung, they are wide and made up of loose, rather acellular connective tissue.

The main histological changes to be seen in the lungs of a normal foal which has respired freely for some time after birth are the disappearance of the cuboidal epithelium about the capillaries and the generally much more irregular character of the alveolar patterns since some alveoli have a tendency to collapse whilst others are very distended. There is no distinct epithelial lining of capillaries, spindly nuclei adjacent to their walls occur regularly and the vessels usually contain a row of one or at most two red cells side by side.

The interlobular septa are reduced to relatively insignificant dimensions.

In the lungs of all the barker foals we have seen extensive "collapse" of the alveoli has been the predominant feature. There is a lack of normal alveolar patterns over very wide areas and in these many of the air spaces where gaseous interchange occurs are completely obliterated, in fact "patency" appears to end in the alveolar ducts. At first sight there appears to be considerable congestion of the alveolar capillaries but when they are looked at more closely the appearance of congestion is seen to spring from "alveolar collapse" which results in capillaries lying side by side; there are not more red cells per unit area of vessel than in the normal new-born. The effect of all this is to reveal a great sheet of comparatively solid cellular appearance when sections of "barker" lung are viewed microscopically.

Many of the atelectatic areas are "dry" but in most cases there are irregularly distributed areas of patchy fluid accumulation varying in staining intensity from a delicate to bright eosinophilic pink. We have not seen hyaline membranes against the wall of air spaces.

In two cases dying within 36 hours there were accumulations of leucocytes at scattered intervals and in several instances there has been some desquamation of bronchiolar epithelium, without evidence of an inflammatory response.

Particularly in those dying within 48 hours there has been a greater persistence of initial epithelium than is usually seen and associated with the collapse the interlobular septa are more prominent than in a normal foal of similar age.

The squame-like structures are about as easily found in barkers as in non-barkers of the same age and only one case showed any increase in pigment content. Haemosiderin has never been found in any lung and, as compared with the lungs of normal foals, no difference has been found in the amount and distribution of the elastic tissue.

In the Malpighian corpuscles of the spleen there is a variable degree of depletion of the cellular elements which are replaced by a hyaline, acellular, eosinophilic material. In some cases this progresses to a very marked degree and we have seen spleens where

practically all the lymphoid tissue has disappeared and the Malpignian bodies appear as structureless, necrotic nodules. The significance of this change is uncertain.

The liver and kidneys have never exhibited any significant lesions and the adrenals have always been quite devoid of any pathological changes.

We have examined sections stained by haematoxylin-eosin and by Einarson's gallocyanin from many parts of the brain. The study of these is not concluded but so far we have not recognised any definite primary lesions. Nor would we expect any great change in the C.N.S. since the recovery is so complete and recovered animals are invariably left with no permanent disability. There are certainly no inflammatory foci; except in one or two isolated instances where they were very minute, we have not detected leakage of red cells, or fluid, from the capillaries. We have not found any neurones which could be described as irreversibly damaged, the nuclei are normal in appearance and position and any alterations in the Nissl substance have not exceeded the changes described in cells where regeneration is expected. There is no apparent glial proliferation.

Discussion

Although expensive foals are sometimes involved and cases prove very irksome on studs because they immobilise labour when every hand is needed, the syndromes are of relatively minor economic importance. Probably the main interest lies in the possibility that some important facts concerning neonatal physiology might be learnt from them.

A wanderer or barker appears to have suffered a violent "blow." It is almost as though a vulnerable group of neurones had been damaged by a sudden alteration in their normal environment, the deprivation of an essential substance, low blood pressure or anoxia. The cases which commence at 12 hours are at present the hardest to understand although delayed clinical effects of damaging processes (anoxia, for example) are well recognised in medical pathology.

Many inborn reflexes are exhibited and utilised by the new-born foal as soon as parturition is completed. Some of these appear in sequence; gasping occurs during delivery and a respiratory rhythm is frequently established whilst the umbilical cord is still intact. Postural reflexes, particularly the "righting reflex" may appear within minutes, the sucking reflex is often seen before the foal is aware of the location of the udder; visual, auditory and olfactory stimuli are appreciated very quickly and when all these are functioning a "normal" behaviour pattern with characteristic actions, affinities and fears is established.

In the barker and wanderer some factor temporarily suppresses reflexes at various levels, this in turn leads to marked alterations in the foal's behaviour and various physiological (and ultimately pathological) effects occur coincidently or soon after. Just where the lung lesions fit into the picture is difficult to say at present. In a less valuable species we should, by now, have made a *post-mortem* examination within a few minutes of the onset of the convulsions, but this has never been possible in our cases.

However, the factors which control the normal initial expansion of the lungs are by no means fully understood. It is most probable that blood volume, linked with blood pressure, cardiac output and vascular resistance are directly and indirectly very important in the process and it is far from inconceivable to us that the lesions could be a result of gross deprivation of the newborn of placental blood.

We may recapitulate some of the salient features associated with the syndromes:—

They are confined to the horse and nothing similar has been described in the other domesticated animals.

Irrespective of considerations of horse populations in different areas, they appear to be of restricted geographical distribution.

They are seen only in Thoroughbreds and, so far as we have yet determined, in those where some sort of human interference is practised at parturition: presumably these facts offer clues to the aetiology.

Hereditary factors could be conceded as possible but improbable influences because of the relatively close relationship of Thoroughbreds in many parts of the world and infection or mineral deficiencies would hardly affect a breed selectively.

When the various possibilities are pursued it is found that a great point of difference, both from the geographical and species point of view, is in the management of the parturitions. An extreme contrast to Newmarket exists in the large Thoroughbred breeding centres in Australia; there the disease is unknown and although mares foal unattended in large paddocks, only a few hours elapse before the foal is examined. It seems inconceivable that such striking syndromes, if they occur, could have escaped the notice of veterinary surgeons and breeders.

If the events during an "assisted" foaling are contrasted with those seen when no interference takes place the major point of difference would appear to be the large deprivation of blood which so commonly accompanies the former, but other less obvious factors may be involved.

Barcroft (1946), Potter *et al.* (1949), Smith (1945) and others have discussed the effects of early and late clamping of the cord and the consequent blood deprivation which occurs in human babies following the former procedure. Most observers are prepared to admit the possibility that undesirable effects might result from this practice, but no definite syndrome arising from it has ever been described. However, compared with the baby, the foal is very mature at birth. It is naturally capable of, and indeed exhibits, remarkable activity within a short time. That so many Thoroughbred foals can be deprived at parturition of as much as 1,500 c.c. of blood (at least 25 per cent. of the normal blood volume) without any apparent clinical effect seems more astonishing to us than the possibility that a few may be harmed.

This is a very vital period for the newborn. It must very quickly establish a pulmonary ventilation which will ensure a much higher level of oxygenation, both in the brain and peripherally, than was present

in foetal life. Sudden and quite premature severance of the foal from its placental reservoir, coincidently depriving it of large quantities of cells and fluid in the initial phase of lung expansion might surely be deleterious to some individuals.

For the immediate future we have planned work with the following in view:—

(a) We intend to verify that the syndromes are confined to mares subjected to human interference at parturition: in this connexion we expect to make personal observations in horse-breeding centres in other parts of Europe.

(b) We hope to institute field trials in the Newmarket area which are designed to test the hypothesis that procedures leading to early rupture of the cord are of significance.

(c) We aim to try to produce a barker experimentally in a non-Thoroughbred.

(d) We propose to attempt to reproduce similar effects in other species.

In preliminary experiments in this connexion we appear to have provoked quite similar lung changes to those of barkers in full-term rabbits deprived of placental blood during caesarean operations.

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THE SPEAKER'S INTRODUCTION

Mr. L. W. Mahaffey began by outlining the story of the investigation. When he had first gone to the Equine Research Station at Newmarket he had not read Reynolds's report but had noticed occasional reports on convulsive and wandering foals in *The Veterinary Record*. They had seemed to be non-existent in the breeding communities in which he had previously worked and others of which he had a good deal of knowledge. In his first Newmarket foaling season he was provided with two foals that had had convulsions soon after their birth. *Post-mortem* examination revealed in both cases widespread and striking changes in the lungs both of which felt extensively consolidated. When the thorax was opened the lungs were very bluish but quickly assumed an angry looking red colour. Subsequent histological examination showed quite definitely that there was no pneumonia. In those two early cases, the essential character of the lesion was seen to lie in the extensive alveolar collapse occurring over very large areas in both lungs. In fact, the normal areas were confined to the apices, the tips of the cardiac notch and the general peripheral areas of the lungs.

Despite a search for sections which might have been kept from previous cases only one could be found, but in it he and his colleagues had immediately come across the same histological lesions—no pneumonia and widespread alveolar collapse. In view of that, and after a lapse of time they had come to think in terms of congenital disease of the lungs, since not only did it seem feasible that such abnormalities might produce curious noises but it was almost certain that alveolar collapse on such a scale would lead to anoxia which, in turn, might very well be responsible for the convulsions. In any case, there were no other obvious lesions at all. As nothing had been seen in previous *post-mortem* examinations of which there were records the only way in which to tackle the problem seriously was to start with what was available.

Very soon afterwards, as a result of the good offices of Mr. Day and his colleagues, they were able to examine clinically a very acute case. Looking at it quite superficially he had been a little perplexed as (again superficially) he thought that the lungs were dilating normally and that the picture was more one of acute metabolic disease. Biochemical as well as histological studies were, therefore, desirable, no previous reference to such work being discoverable. Moreover, figures for new-born foals were not available. He and Mr. Rossdale had thought they should make some 20 or 30 examinations—or whatever number they could get—and the simplest way to get samples of clotted and unclotted blood seemed to be by asking for umbilical cord blood. They had not thought it likely to prove difficult to get from 5 to 30 ml. of blood, but far from that being a mistaken idea they were both immediately struck by the huge quantity of this sort of blood that was available. Within a week, Mr. Mahaffey had a cylinder containing 1,400 ml. of blood from one parturition alone. That, of course, resulted directly from the extremely precipitate severence of the umbilical cord as practised in so many Newmarket studs.

It had needed very little thought to lead to the conclusion that blood deprivation upon such a scale could hardly be in the foal's best interests. Accordingly, he and his collaborator determined to study the act of parturition very carefully and particularly to concern themselves with the quantities of blood emptied on to the ground or into the buckets as a result of the groom's endeavours. They determined, in addition, to observe the quantities of blood available when an attack on the cord was delayed, or never put into practice at all—a very rare thing. Mr. Mahaffey's personal belief was that the umbilical cord required no human attention at all as it was a fact that everything was provided for naturally in that respect, both as to the appropriate place, morphologically, and the appropriate time. Nevertheless, it was a very rare occurrence in thoroughbred practice for the cord to be left alone.

Mr. Rossdale attended 61 parturitions in the area, while the speaker was present at others in England. He had made extensive enquiries as to the methods used at parturition. He had found that both in France and Italy the practice was similar to that in this country, and he had had no difficulty in determining that the syndromes occurred in thoroughbreds in both of those environments.

Mr. Rossdale would tell the audience of what he had seen during his many nights of interrupted sleep during the spring, and would tell of some significant developments

recently made which might offer some hope of an explanation of the lung conditions found in convulsive foals. After that Mr. Mahaffey would present some interesting slides relating not only to foals but to rabbits which had been deprived in one way or another of varying percentages of blood. A very striking similarity in the lung condition would be seen.

Mr. Rossdale, continuing the story, said that from their observations Mr. Mahaffey and he had come to the conclusion that in the great majority of parturitions in thoroughbreds the cord would, if there were no interference, remain intact from 3 to 10, or even 15 minutes after delivery. That opinion was based on the fact that most mares gave birth whilst recumbent and remained recumbent for from 3 to 15 minutes after delivery. Meanwhile, the foal remained in the position of final delivery, i.e., with the hind legs in the vagina to the level of the hocks for a period of 10 minutes or longer, if allowed to do so.

Finally, the equine cord was relatively long and resisted a high degree of tension. Pulsation could be felt in it for up to 7 minutes after delivery had occurred—the average was about 2 minutes—indicating that there was circulating blood in the placenta during that period. By collecting blood from the severed end of the cord at varying times after delivery it was clear that the method of immediate severance was depriving the foal of up to 1,500 c.c. of blood, or, to put it in another way, 25 per cent. of its blood volume. That finding was in accordance with the recent work of Gunther (1957) who had estimated that the human infant might be deprived of as much as 40 per cent. of its blood volume by similar treatment of the cord immediately after birth.

In order to substantiate the hypothesis that the immediate tying of the cord was in some way concerned with the aetiology of the syndrome under discussion it was necessary, first, to make large-scale field trials, and, second, to try to produce the condition experimentally in equine animals and in other species. The authors hoped to do that but, with an incidence of only 2 per cent. it was obvious that the work would have to be done on a large scale. Their first attempts to produce the condition experimentally in rabbits had been encouraging in that they appeared to have provoked a pattern of alveolar collapse by depriving the foetus of placental blood during caesarean section.

Since the paper had gone to press there had come to the notice of the authors a condition in infants described by Bound (1956), who called it cerebral irritation and described symptoms of convulsions, excessive wakefulness, restlessness and a shrill, high-pitched cry. In 63 per cent. of those cases the only *post-mortem* lesions found were in the lung. There had also appeared in the medical Press a series of communications relating to that syndrome and the pulmonary syndrome of the new-born to premature clamping of the cord at birth. In both syndromes there was a striking similarity in the pathology of the lungs to that found in "barkers."

How, then, could the premature severance of the umbilical cord be related to the lung lesions found at *post-mortem* in "barkers"? A respiratory rhythm in the foal was normally established within a minute of the delivery of the thorax. If the cord were severed before that respiration rhythm was established a profound asphyxia would result at the same time that the foal was deprived of a large amount of its blood volume.

The mechanism of initial lung expansion was not fully understood, but the negative pressure exerted on the lung by thoracic movements was not alone sufficient to cause proper alveolar inflation throughout the lungs. Jäykka (1957) had shown that the capillaries played their part by helping to hold out the alveoli, a result of their erectile nature as they became distended with blood. The erection of the capillaries into a scaffold for the alveoli depended on such factors as cardiac output, blood pressure and vascular resistance. All those factors were directly affected by asphyxia and lowered blood pressure consequent on the premature cutting or tying of the cord.

There was, therefore, continued Mr. Rossdale, clearly a possible link between initial lung expansion and the premature tying of the cord, and, in a syndrome appearing within 24 hours of birth where extensive alveolar collapse formed the major part of the pathology those considerations might surely be of great importance. In conclusion, said Mr. Rossdale, the authors thought that the symptoms shown by affected foals were consistent with those that might be expected where cerebral anoxia was a causal factor.

Mr. Mahaffey then concluded the authors' introduction of their paper with a series of slides in support of their proposition.

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The Opener

Dr. A. C. Fraser (Wokingham), who opened the discussion, thought that the authors had presented a possible—he thought a probable—answer to a particular disease. Yesterday, "barking" foals were completely unaccountable, there were no explanatory hypotheses, and most foals so affected were destined to die. He did not need to stress the signs of the disease to those who had seen the condition but he did know how desperately ineffective a veterinary surgeon felt when called to a foal in what he could best describe as a hysterical coma. Not only had the disease been a headache to veterinary surgeons, but the losses caused by it had been serious for bloodstock breeders to whom its elimination would be of direct cash value.

He wished to emphasise most strongly that in the 1957 foaling season they had known of no treatment for the convulsive condition other than the use of sedatives to mask the symptoms and quieten the foal. They had not known how the disease was caused and if, or how, it could be prevented. Now, the authors might have opened the door to the solution of all those problems. The disease might possibly be preventable and curative treatment, as a result, not of the greatest importance. About that, however, he intended to ask the authors a question later.

He wanted those present to appreciate the work done, as it had revealed in the authors an infinite capacity for taking pains. A careful reading of the paper would reveal that their conclusions had been reached only after much hard work, endless inquiries and the exploration of avenues many of which had led nowhere at all. Mahaffey and Rossdale had to be praised because, although they had presented their work in a modest way they had supported it with such a mass of evidence that he thought their conclusions were tenable. If those conclusions were correct, the disease might disappear completely from the list of perils that beset the stud farms—and he could think of no better way for the essayists to earn congratulations and deep gratitude.

Apparently, after the normal birth of a foal there was pulsation in the intact umbilical cord for a period of up to several minutes, and during that time a quantity of blood flowed from the placenta to the foal. If the foal was deprived of that considerable quantity of blood which, emphasised Dr. Fraser, it should receive from the placenta after actual birth, it was likely to develop nervous signs and a peculiar atelectatic condition of the lungs.

A tradition had grown up among stud grooms that the cord had to be cut, disinfected and tied immediately the foal was born, and they took pride in completing that job in record time. Such a responsibility might have been laid on them in the past by veterinary surgeons with the fear of navel-ill infection in mind, and Dr. Fraser had every sympathy with those stud grooms who sat up night after night to ensure that no accident occurred at the time of birth, and who were very ready at any minute to render the mare and foal those first aids which, it would now seem, it became the duty of veterinarians to persuade them to postpone.

By a coincidence, since the essayists commenced their work, considerable interest had been shown in human medicine in a similar phenomenon occurring in new-born infants. In the medical journals there had been a lively correspondence. The authors of this paper had joined in it and their

contributions had been appreciated and acknowledged by their medical confrères. In many ways the pulmonary syndrome of the human child—resembling in a variety of ways the conditions under discussion—was a frequent cause of infant mortality and was connected with the retention in the placenta of a quantity of blood that should have been transferred—after the actual delivery of the child—to the infant's circulation. Emphasis was placed on the danger of interference with the natural process of birth. Mavis Gunther, writing in *The Lancet*, had drawn attention to the fact that the baby born before the arrival of assistance thrived. Since it usually lay below the level of the placenta, the tying of the cord did not immediately take place and the warm blood had time to gravitate to the infant in the period during which pulsation continued in the cord.

Continuing, Dr. Fraser said that the dangers of early interference with the umbilical cord had long been recognised in human genetics but he doubted if support from the medical profession for the theories of Mahaffey and Rossdale could be summarised more succinctly than in a quotation from Erasmus Darwin—father of Charles Darwin—who, 156 years ago, had written: "the navel string should not be cut until the child has repeatedly breathed and all pulsations in the cord ceased, as otherwise the child is much weaker than it ought to be, a part of the blood being left in the placenta that ought to be in the child."

Correspondence in the medical journals accepted the principle that early section of the cord was dangerous, but they were not agreed why such interference produced disease. Bonham Carter maintained that it was the additional volume of blood reaching the infant which was important, while R. J. K. Brown, agreeing that section of the cord ought to be delayed, believed that early section caused a dangerous rise of blood pressure in the infant with effects that caused damage to the tissues and produced the signs of disease.

The authors of the present paper, having suggested the cause and prevention of "barking" in foals were anxious also to penetrate into the true explanation of the peculiar conditions of the lungs of foals that had died of the disease. They wished to know whether, for instance, intragastric oxygen would be of help, as it was to babies suffering from a similar condition—and Dr. Fraser confessed that he was interested to know if Mahaffey and Rossdale thought that that had any advantages over the subcutaneous approach which was so easy in animal patients. They were also interested in whether a similar syndrome could be produced, or could occur in other animals, and the first of the two questions which he would like to ask was: what steps should a general practitioner take if, in spite of educating the stud grooms in his area, he came across a "barking" foal or a "wanderer"? Though his second question rather led away from the convulsive syndrome the essayists were so closely interested in the process of equine birth that they might have the answer already. How were cracked ribs to be prevented or, to put it another way, how were they caused during the act of foaling? Were they also caused by over-enthusiasm on the part of stud grooms? Cracked ribs, pointed out Dr. Fraser, and the pericardial effusion which sometimes accompanied them used to be linked together as the cause of sleepy foals. It was now known that the sleepy condition was a sign of infection. Cracked ribs had also been associated with "barkers" but it was now known that they were not responsible. So unusual was it to make a *post-mortem* examination on a new-born foal without finding evidence of greater or less damage at the costochondral junction that he wondered if cracked ribs were inevitable in the present state of development of the thoroughbred. If so, was the mare's pelvis or the foal's thorax responsible? Again, did cracked ribs in foals which survived interfere eventually with the foal's racing prospects?

Finally, Dr. Fraser congratulated the essayists on an example of co-operation between the laboratory worker and the clinician. That was a trend he was glad to see developing, and it had to go on developing as increasing specialisation divided one group of veterinary surgeons ever more widely from another. The paper was likely to be of great value to the bloodstock industry and to the general practitioner. It also increased the high reputation of the research workers in the profession, and of the Equine Research Station, without which that particular piece of work would never have been been undertaken.

The General Discussion

Mr. J. L. Hancock (Edinburgh) said: "Three or four years ago Dr. A. D. Bangham, of Babraham, suggested to me that cerebral anoxia might be a cause of neo-natal death in young animals. I believe that one of the known causes of cerebral anoxia in the new-born infant is premature separation of the foetal membranes *in utero*. If this is true of the foal it would be unwise to assume that the "barker foal" syndrome will disappear even if stud grooms can be persuaded to discontinue the practice which Mahaffey and Rossdale have shown to be hazardous.

Mr. E. Brayley Reynolds (Newmarket) wished to congratulate the writers of this paper on the great efforts they were making to solve this most puzzling condition, which to his knowledge had caused the loss of thousands of pounds worth of thoroughbred foals in the last 35 or 40 years. He wished them success in their work. It was particularly pleasing to him that this work was being undertaken. There was one question he would like to ask: if they were correct in the view put forward, that the deprivation of a large volumn of blood resulting from the present method of dealing with the umbilical cord immediately after birth was the cause, how did they explain the very small number of foals affected out of the very large number that were dealt with in precisely the same way?

The Reply

Mr. Mahaffey, who undertook the task of replying, said that those who had read the paper would appreciate that neither he nor Mr. Rossdale by any means accepted what they had presented for consideration as a *fait accompli*. They suggested only that there was a probable connexion. In addition, irrespective of "barking" and "wandering" they believed it could not be a good thing for any new-born foal —which was born in such a state of maturity that sometimes it could not be caught five minutes after birth—to be deprived of anything from 1,000 to 1,500 c.c. of the placental blood which it ought to get. It was therefore hoped that, as a result of the paper, the foals would get their placental blood. Better health might result, as there was a large quantity of corpuscles, fluid, iron and the like which otherwise took a lot of making up. He was quite sure that not a single practitioner in the room would give him permission to take a litre of blood from a new-born foal, whether or not it had had its placental blood, yet by allowing the stud groom to cut the cord within seconds—the most precipitate cutting in the whole animal kingdom—they were condoning the selfsame thing. That was all he and Mr. Rossdale wanted to stop, and during the next 2 or 3 years they would watch to see if the incidence of "barkers" was the same. If it was, then they would think again.

Intragastric oxygen was used extensively in human medicine, but the authors' theory was that once the syndrome existed such treatment was no good at all. At the moment they could not tell why, but they thought that something happened at the very moment deprivation took place. Nor did they know what steps a veterinary surgeon should take with a "barker" if he had insisted upon a delay in severing the cord. He and Mr. Rossdale would have to agree with Mr. Day and say that the best treatment appeared to be mysoline.

Mr. Mahaffey did not know the cause of cracked ribs, but he thought they must have some connexion with assisted parturition methods in England, as they were much more prevalent here than in Australia and New Zealand. He did not think it *so* unusual to do a *post mortem* and not find cracked ribs. His own experience in England had been an incidence of 20 per cent. or under.

Mr. Day had asked how, if the hypothesis put forward was correct, an anti-convulsant could do the trick. Mr. Mahaffey confessed that he had not the answer to that question, but it did not in any way offend him to think that mere rest, or control of convulsions could in some way

allow of a stabilisation of the physiological processes involved. It was all very vague, but he was sure that if the convulsions were allowed to go on the foal would die from exhaustion. As in some other conditions of "disturbed physiology," if the foals could be kept in control they might spontaneously rectify the condition. Some years ago Mr. Leader had said that there were often survivals merely as a result of holding the foal down until the convulsions ceased.

Mr. Reynolds had suggested that the whole syndrome might be due to some defect of the circulation in the brain, consequent upon a bruised heart. Forgetting for the moment the bruised heart, his remark that it might have something to do with the circulation in the brain was possibly near the mark. Mr. Reynolds had asked why, if the whole syndrome were due to blood deprivation there was such a small percentage of "barkers." That, too, was very difficult to answer, but it was known, of course, that there was an inherent variation in individuals. He himself understood that the "pulmonary syndrome" in babies was a rare condition, but, after all, were "barkers," "wanderers" "dummies" and similar foals so very rare? An analogy for the percentage would be as follows. If one were to bleed out a number of animals, at a certain point there would be 100 per cent. deaths. Below that point there would be some survivors, and the number of survivors would increase as the bleeding decreased, but why some and not others should survive at any one point was more or less a physiological secret.

Dr. Hancock's remark was very much to the point. Mr. Rossdale and Mr. Mahaffey had for a long time been thinking of the possibility of a premature separation of the placenta *in utero* as playing a part in the syndrome, and that might have something to do either with all "barkers" or with some of them.

Mr. Short had asked if anyone had thought of transfusion, but Mr. Mahaffey's opinion was that once the thing had been set in motion some physiological event took place which might be difficult to alter quickly. They had not yet done any work on that. That was his answer also to Mr. Cosgrove. Mr. Mahaffey did not think that 500 c.c. of blood put into the pectoral muscle would be of any value in connexion with the particular syndrome. Nor had they used any drugs other than mysoline.

Mr. Crowhurst had been very rightly sceptical, but Mr. Mahaffey had not found any similar condition except in man. In a letter in *The Lancet* (July 13th, 1957) the authors had made the very point that, by coincidence or otherwise, only the two species subject to human interference at parturition got the "pulmonary syndrome," and there was no doubt that there were striking similarities to that condition. Again, Mr. Mahaffey had little doubt that the geographical distribution described in the paper was correct, but if as a result of describing their cases and theories others came to light from, say, Australia or New Zealand that would only add to the knowledge of the subject and this was the authors' objective.

Some Diseases of Suckling Pigs

BY

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Introduction

THE object of the present paper is not to catalogue the known diseases of the suckling pig; but rather to discuss some of the topical problems in this field. Thus the account that follows is largely derived from personal experiences of piglet morbidity in East Anglia and in some measure, therefore, it indicates the current concern of a group of practitioners who, by tradition, administer to a large number of pigs.

The diseases that follow are necessarily limited in number and they have been selected either because they have been studied in some detail by the writer or because they are problems that warrant clinical comment at the moment. In the former group are hypoglycaemia, avitaminosis A, haemolytic disease and, to a lesser extent, trembling, and with these conditions the opportunity has been taken of presenting a short review of present knowledge. With the other diseases, no attempt has been made to relate the present observations to the literature, because only certain aspects are touched upon in each case.

Hypoglycaemia and "Baby Pig Disease"

Graham, Sampson & Hester (1941) found that severe hypoglycaemia was a common finding in new-born pigs dying without other evidence for the cause of death and this entity they described as "Baby Pig Disease". Subsequently, they made the important and interesting observation that starvation alone could readily induce hypoglycaemia (Sampson, Hester & Graham, 1942), although as the pig became older it became increasingly refractory to starvation (Hanawalt & Sampson, 1947a, b) and by the time it was 10 days old it could survive without food for about 3 weeks. It was later suggested (Morrill, 1952) that the term "Baby Pig Disease" should be avoided, particularly when a specific cause of death was known, but in Britain there is still some confusion. The term is in wide use and inevitably, if it has any specific meaning, which is unusual, this varies from one person to another. Furthermore, by continuing to use the term for diseases of unknown aetiology the more fundamental implications of the original Illinois work are masked. The new-born pig must eventually exhibit hypoglycaemia whenever its nutrition is severely interrupted, regardless of the primary cause, and hence some degree of hypoglycaemia with all its attendant disadvantages will be an extremely common sign in the very young piglet (Goodwin, 1955). What is equally important from the clinical point of view is that the piglet exhibits a second deficiency consequent upon the development of hypoglycaemia. Not only is the piglet peculiar among farm animals in being unable to maintain its blood-glucose concentration when starved—the new-born lamb (Sampson, Taylor & Smith, 1955), calf and foal (Goodwin, 1957a) being much more resistant in this respect—but a falling blood-glucose concentration in this species produces a concurrent decline of over-all body function. Thus the heart rate, body temperature, respiratory rate, etc., of the new-born pig all collapse as the blood-glucose concentration falls (Goodwin, 1957b) and there is superimposed upon many different diseases a blanket of common signs; those of complete collapse. It is not surprising, therefore, that the clinician should find differential diagnosis unusually complicated. It is of interest that whereas the temporary metabolic weaknesses of the young piglet suggest a possible deficiency of adrenal function, it has not proved possible (Goodwin, 1956, unpublished experiments) to ameliorate either the deficiency of gluconeogenesis or the total body collapse during hypoglycaemia with injections of cortisol.

Vitamin A Deficiency

It has been reported in the literature that varying degrees of vitamin A deficiency in the sow will produce a graded series of defects ranging from anoestrus, a failure to conceive and foetal resorbtion, to still-births with gross deformities, congenital blindness, neonatal death, or, later still, a predisposition to intercurrent infection (such as enteritis) and nervous signs in suckling pigs. Without contesting the probability that these consequences occur, it must be admitted that some of the earlier work would be open to alternative interpretations. Thus a variety of deficiencies (see Giroud, 1954; Warkany, 1954) and other factors may interfere with foetal development, and following upon the work of Young (1952) evidence has been accumulating that infections of the sow during early pregnancy can have a similar effect. Hence pathological descriptions of foetal abnormalities should be related to a specific aetiology if they are now to be of value in differential diagnosis. It is against this background that debate has recently centred (Harding & Done, 1956; Watt & Barlow, 1956b) on the varying causes of microphthalmia in the new-born pig. Ideally, when piglets are suspected of being nutritionally deficient, they should be shown to be so chemically; and to show that no other deficiencies are involved, the pathological changes should be prevented by feeding the same basic diet supplemented with the missing nutrient. Inevitably, few accounts of vitamin A deficiency in the past have attained these standards, because at first there was little knowledge of the different vitamins and secondly, it is only comparatively recently that pure vitamin A has become available. In addition, it has often proved difficult to investigate adequately naturally-occurring cases in the field. However, Hale (1935) produced blind and deformed piglets with a deficient diet that was made adequate by the

addition of cod liver oil alone and more recently Bendixen (1950) repeated these experiments but improved the diet with green food. Bendixen wondered whether a deficiency of vitamin A alone was involved and introduced the complication of a concurrent deficiency of vitamin D, a point that would also apply to the work of Hale. The experiments of Braude, Kon, Mitchell & Thompson (1951) were more conclusive. They produced weak and moribund piglets that were shown to be deficient in vitamin A, while control gilts given cod liver oil produced normal piglets. The latter authors, unfortunately, provided few anatomical details of the condition produced and despite the fact that microphthalmia associated with a possible nutritional deficiency is not rare among pigs (Hale, 1937; Smith, Robinson & Bryant, 1938; Sandstedt, 1943; Bendixen, 1944, 1950; Marcq & Hennaux, 1946; Pulsford, 1949; Eden, 1949; Bauer, 1950; Maneely, 1951; Hubrig, 1954; Schoop, 1955; Watt & Barlow, 1956a) there appears to be no detailed account of the over-all pathology of avitaminosis A in the new-born.

During 1956 four herds were examined in which piglets were dying shortly after birth or, although viable, were showing microphthalmia. Altogether, at least twenty-one litters suffered heavy mortality and a further eleven or more litters contained piglets that showed a variety of eye defects. A diagnosis of avitaminosis A was reached in each instance, and detailed clinical and pathological observations were made on the piglets in the first two herds, where the diagnosis was more reliable. The findings have been reported in full elsewhere (Goodwin & Jennings, 1958) and the following remarks, which emphasise the clinical conclusions, are taken from this work.

That the various pathological changes were brought about by a deficiency of vitamin A was indicated in several ways. First, the diets of the affected sows were deficient in vitamin A and there had been no access to green food during part or all of pregnancy; in many instances this lack of green food had been virtually complete since the birth of the breeding animals. In one herd there were some animals that had received vitamin A in their diet and these, in sharp contrast to the deficient animals on the same premises, produced normal litters. The effect of improving the diet was most striking in the first herd examined, because the severity of the condition progressively declined once vitamin A was incorporated. That is, whereas many litters had died previously there was a period after the diet had been fortified when piglets were born viable but blind and then, later still, all further litters were completely normal. Further evidence for vitamin A deficiency was provided by liver analyses at birth, but the most conclusive support derived from an experimental study in which four sows were rebred and kept on the original deficient diet. Two of these sows received vitamin A palmitate in their ration before service and during pregnancy. They produced normal litters, whereas all the piglets from the untreated pair of sows died shortly after birth.

In the most severe form of the disease the piglets were born at full-term but were either still-born, when they occasionally showed severe ascites, or very weak so that they died within a few hours. They were generally of normal size and never showed external deformities, such as described by Hale (1935), except for eye defects. Goliarkin (1941) also speaks of abnormally developed piglets but other authors have found little external deformity and it would appear that too much diagnostic emphasis could be given to Hale's findings. Thus Pullar (1950) tended to rule out a deficiency of vitamin A in his cases because no deformities occurred. Indeed, as dead piglets presented for routine investigation would usually have closed lids there might be very little to indicate avitaminosis A if the lids were not opened. The live-born but non-viable piglets showed varying degrees of weakness: some just lay on their sides around the hindquarters of the sow unable to get to their feet. They paddled the air almost continuously and squawked plaintively. Such squawking by many weak pigs in a litter became somewhat characteristic. Slightly stronger piglets crawled on their abdomens away from the sow and showed little or no interest in suckling; there was also a marked tendency for them to burrow and hide under the bedding. Moribund piglets showed evidence of circulatory embarrassment and, probably as a result of this, the skin lacked tone and did not dry off properly; hence amniotic flakes adhered to the body. Sometimes subcutaneous oedema gave the animals a rounded appearance. When the necessary examination was made, all the naturally-occurring cases of this type had eye defects. The lids were often gummed together with a brown wax-like material and the eyeballs were either bulging and cyst-like, or vestigial. There was commonly severe entropion.

When the condition was less severe the pigs were more vigorous at birth and appeared normal except for gross eye defects similar to those seen in the still-born pigs. But in a less severe form still, there was no involvement of the lids and the eyeball was of normal shape and size, the defects being mainly in the position and extent of the iris. Piglets that were vigorous at birth were usually reared, although in some instances the deficiency appeared to worsen by about 3 weeks of age. It was said that the animals had nervous fits before death, but the pigs that we were able to examine showed only paralysis and they were very similar to those produced by Nordfeldt (1945). It might be mentioned here that we have encountered a poliomyelitis in suckling pigs in East Anglia that is histologically and clinically similar to the paralysis described by Bendixen & Sjolte (1955) in Denmark. Pigs showing this type of posterior paralysis were not obviously different clinically from the pigs that dragged their hind legs from avitaminosis A, but although the central nervous system in the latter condition showed demyelination in the cord, particularly in the lumbar area, and also slight demyelination in the cerebellar peduncles, there was no perivascular cuffing or glial accumulation which would indicate an encephalomyelitis.

The internal *post-mortem* examination of the new-born pigs generally revealed a great deal of fluid, which infiltrated the subcutaneous tissues and dis-

tended the body cavities, particularly the pericardial sac. In still-born pigs there was striking liver damage and as there was often abundant fibrin on the peritoneal surface of this organ and also petechial haemorrhages on the heart, we were led at first to suspect an infective aetiology. Abnormalities, particularly of the kidney, were not uncommon. The histological appearance of many of the body tissues are given in the original paper but apart from the severe and generalised oedema the changes in the epithelial surfaces can be singled out. Here there was proliferation and vacuolation but no metaplasia. Thus it seemed that in the foetus there was no progression to the differentiation seen in the adult.

Two further points merit comment. First, having seen many pigs born blind but viable in the field we had come to the conclusion that if a pig were to be born dead with no vitamin A in the liver it would be unlikely to have normal eyes and, therefore, an examination of the eye would be of particular value in clinical diagnosis. However, in two litters produced experimentally, where all the pigs were dead or moribund at birth and where the livers examined contained no vitamin A, all the eyes were quite normal, even on histological examination. There may have been special reasons for this occurrence, and these are described elsewhere, but in keeping with the findings of Braude *et al.* (1951) it demonstrates that such an event can be expected. The second point concerns the dams. These were nearly always gilts, which is a point stressed by others and accords with the fact that the reserves of older sows are not readily depleted (Braude *et al.*, 1951). In none of the many gilts and sows examined was there any striking clinical sign of vitamin A deficiency.

Trembling

This disease of the new-born pig is well known (Kinsley, 1922; Nissley, 1932; Hughes & Hinman, 1936; Knilans, 1936; Hindmarsh, 1937; Glässer, 1950; Kernkamp, 1950; Lamont, Luke & Gordon, 1950; Fankhauser & Wyler, 1953; Brooksbank, 1955; Larsson, 1955; Christensen & Christensen, 1956; Goodwin & Palmer, 1956; Hupka & Horn, 1956; Stromberg, 1956; Turbes, Richards & Abreu, 1956). The condition in France described as "Tremblements", however, (Payen, Ballot & Fournier, 1934; Florio, Flachat, Cottereau, Flochon, Fedida & Saint-Cyr, 1956) appears to be a different entity. For several years the writer has been observing large outbreaks of trembling in the hope that such abundant material might point to a common underlying aetiology. Although this work has not been very fruitful, it has produced a number of epidemiological observations that can be summarised here. The first is that although many piglets in a litter are commonly affected it is also possible to find a single severely-affected piglet in an otherwise normal herd and it is difficult to reconcile the known aetiological possibilities with such a discriminating effect. Secondly, the disease is not rare. It is probably made less obvious, however, by the tendency of some farmers to ignore it and by the unfortunate fact that pedigree breeders feel it could indicate a hereditary defect in their stock. Thirdly, none of the cases examined to date provide any evidence for such a hereditary defect. Thus in a very large outbreak in a big herd the affected litters are born from unrelated sows and may have been sired by a number of boars of different breeds. Furthermore, in agreement with the experiments mentioned by Larsson (1955) but in contradistinction to Hupka & Horn (1956), trembling piglets kept for breeding have always produced normal litters.

The fourth observation is that when a large number of litters are affected they are born in close succession, often with only a few unaffected litters interspersed. That is, the disease appears suddenly, the affected litters are concentrated over a varying period of time, and then all further litters are once more normal at birth. Such a disease pattern is highly suggestive of a common environmental factor operating during pregnancy and Brooksbank (1955) has suggested that this factor might be a virus infection such as swine fever. Although it is difficult to rule out such a possibility in the field, the author's outbreaks have not been associated especially with swine fever and there has more often been evidence of a grossly unusual diet during pregnancy, which in company with the reports of Knilans (1936), Glässer (1950) and Christensen & Christensen (1956) favours a metabolic or deficiency condition in the piglet. However, there could be more than one aetiological factor, as has been seen with microphthalmia, and outbreaks have occurred where the diet appeared normal. The fact that most severely-affected piglets appear to recover completely in a few weeks suggests that either there is permanent damage that is compensated by post-natal development, or that a temporary functional deficiency is made good after birth. It is noteworthy that this improvement is initiated when the piglet is receiving only sow's milk.

Another observation of interest was made following the sale of gilts from a large pedigree herd. Many of the sold gilts together with those remaining on the original farm produced trembling piglets and, in all, over one hundred litters were affected on widely dispersed farms. Trembling occurred even when the gilts at purchase were less than 1 month in-pig and hence the dams must either have been conditioned before the sale or carried some agent with them capable of damaging the foetus. The final observation is that often when trembling litters are being born many of the piglets are small and weak; hence it seemed possible that there might be a more severe form of the disease. Evidence for such a view has been seen in a herd where nearly all the piglets in eight litters, farrowed over a period of 2 months, were born dead or died within a few hours. It was said that in four of the litters the live-born piglets showed trembling before death and the three piglets that survived were certainly typically affected.

Histological changes have been described in this condition such as some rounding of isolated muscle fibres (Lamont *et al.*, 1950), cell degeneration in the corpus striatum (Brooksbank, 1955), incomplete development of myelin sheaths (Christensen & Christensen, 1956) and pigment infiltration with Purkinje-cell degeneration in the cerebellum (Turbes *et al.*,

1956). My colleague A. C. Palmer has examined the brains and spinal cords of seventeen of our recent cases and compared them with similar sections from nine apparently healthy animals. So far no abnormality has been found consistently in the material from the affected pigs.

Haemolytic Disease

The first account of haemolytic disease in the newborn pig was based on cases that had been produced experimentally (Bruner, Brown, Hull & Kinkaid, 1949), but field reports of the condition soon followed from Hungary (Szent-Iványi & Szabó, 1952, 1953), Britain (Buxton & Brooksbank, 1953a, b) and the United States (Doll & Brown, 1954). Whether the disease as seen in the field occurs spontaneously, however, has not been resolved; for Goodwin, Saison & Coombs (1955) showed that injections of crystal-violet swine-fever vaccine could readily stimulate the production of red-cell iso-antibodies in pigs. Furthermore, such iso-antibodies were found to be common and often at high titre among pigs that had been vaccinated twice in the field, whereas among unvaccinated pigs they were rare. From this evidence, together with the fact that only two of the many sows with affected litters investigated from Cambridge could have been unvaccinated, it must be concluded that in Britain the disease is largely consequent upon vaccination. As the sow described by Doll & Brown (1954) and also the more recent cases of Newberne, Robinson & Moore (1956) had been vaccinated with crystal-violet vaccine and a splenic tissue vaccine, respectively, it is possible that the disease in the United States is likewise artificially induced. In Hungary, however, the aetiological evidence is less clear-cut (Szabó, Szent-Iványi & Széky, 1956) and it seems that cases might have arisen in litters from unvaccinated sows, although it is not yet known in these instances whether other agents such as impure serum could have supplied a comparable antigenic stimulus. The description that follows, therefore, may not be wholly applicable to conditions outside Britain.

The first injection of vaccine does not usually produce a high iso-antibody titre in the sow's serum (Goodwin, Saison & Coombs, 1955), although deaths from haemolytic disease have been seen when the sow was said, without doubt, to have been vaccinated only once (Goodwin & Saison, 1957). Hence it is the second injection which is usually critical, and the ensuing iso-antibody response varies with several factors, one of which could be the red-cell components of the vaccine. However, as each batch of vaccine is prepared from the pooled blood of many pigs, it is possible that qualitatively the blood-group antigens do not vary greatly from batch to batch. Of the other factors, the constitution of the sow is most important. First, there is a marked breed difference in the response to vaccination (Goodwin & Saison, 1956): when the red cells of Large White boars are used for testing, Essex and Wessex sows nearly always demonstrate some iso-antibody, whereas Large White sows may often be vaccinated repeatedly without providing a detectable response. It does not follow that Large White sows do not produce iso-antibodies that would be detected by red cells from Essex or Wessex boars, but if this proved to be so it would be of purely academic interest; for Large White sows are not in practice mated to such boars. The second main influence exerted by the sow relates to the strength and duration of the antibody response. There is some evidence (Goodwin & Saison, 1957) that the level of antibody produced is innately characteristic, so that in any particular herd there might be only a predetermined group of sows capable of producing high iso-antibody titres. The duration of the antibody response also appears to vary markedly from sow to sow and two main types of response have been observed. In many sows the iso-antibody titre reaches a peak shortly after vaccination and then declines away to a low level in a few months; in others, however, the antibody titre can remain at a high and fairly constant level for several months or years without further vaccination and in the absence of gestation (Goodwin & Saison, 1957). Clearly, sows with the first type of response will damage their litters only if they farrow while the antibody titre is still high; but sows of the second type, if mated to suitable boars, could become conspicuous by repeatedly losing their litters. This latter situation has been commented on as a feature of the disease in Hungary (Szabó *et al.*, 1956).

The incidence of the disease, therefore, is governed in the first place by the response of the sow. It would be expected that cases would be much more common among Essex and Wessex sows than among Large Whites and this is so in practice; all but three of nearly fifty affected sows investigated from Cambridge being of the former two breeds. Most affected litters have been from Essex/Wessex x Large White crosses but a few cases have also been seen from both pure Essex and pure Wessex matings. The lack of cases among white sows is most striking, no case being seen among pure Large Whites and only one affected litter being known in the Landrace breed. As among the numerically small Large Black breed two sows are known to have lost litters it does appear that there might be a sharp difference in blood-group antigens between the entirely-white and largely-black groups of pigs. That the Large White breed, at least, might be antigenically nearly homogeneous is supported by the results of Goodwin & Saison (1956). They found that a high percentage of red-cell samples from Large White boars registered a similar titre against a serum sample from each of two sows that had lost litters with haemolytic disease. It follows from this that an alternative Large White boar will not often provide a compatible mating once an Essex or Wessex sow has lost piglets with the disease, and this is borne out by the repeated loss of litters when such alternative matings have been tried in the field.

It is difficult at this stage to assess the economic effect of haemolytic disease. Very many sows produce iso-antibodies after vaccination but fortunately, in most cases, the antibody level is not high enough to be lethal. For every litter that dies, therefore, there are several that are markedly affected and suffer a steep fall in haemoglobin concentration only to recover without attracting attention. This wide sub-

lethal and subclinical background to the disease is one of the main aspects of its epidemiology and, as has been stressed elsewhere (Goodwin, Hayward, Heard & Roberts, 1956), many affected litters survive because the new-born pig can withstand remarkably well a sudden loss of red cells. Thus it has been proposed by the same authors (1955) that unless the maternal iso-antibody can reduce the piglet's haemoglobin concentration to about 3 g. per 100 ml. by 72 hours after birth the animal will recover. Nevertheless, there are reasons for believing that many deaths from haemolytic disease pass undiagnosed. First, the mortality occurs during the first three or four days of life, at a time when there is much other mortality of confused aetiology. Secondly, although the disease frequently destroys whole litters it may also kill only part of a litter, and then it is less obvious. Thirdly and more pointedly, very few cases have been reported to the writer as haemolytic disease from the field; that is, most of the sows with clinically affected litters so far examined have come to our notice rather fortuitously. This chance uncovering of the condition is well illustrated by the two most recent herds investigated. In both instances the disease was first suspected when dead piglets were examined in routine diagnostic laboratories. With the first litter there was a history of a second litter having died under circumstances very suggestive of haemolytic disease 6 weeks previously, and on visiting the farm not only was the diagnosis confirmed in both these litters but a third litter was seen to be affected. In the most recent instance, a visit to the farm likewise confirmed the fact that another litter had died of haemolytic disease in the same week, and thus from the *post-mortem* appearance of two groups of piglets, five affected sows were identified. There is now a need for earlier recognition of the condition and to this end a simple test has been described (Goodwin, 1957c), which, in conjunction with the main clinical and *post-mortem* signs, should allow in most instances a confident diagnosis on the farm.

Nutritional Anaemia

The hypochromic microcytic deficiency anaemia of suckling pigs is well documented and most cases appear to be due to an iron deficiency, although there are other theoretical causes of doubtful practical incidence. In the author's experience the entity is now comparatively uncommon in the field and this may be due in part to the present widespread use of artificial anti-anaemia measures of various types. Indeed, the quantity of iron administered to some litters is alarming and in one herd recently a marked enteritis occurring at about 3 weeks of age ceased as soon as the excessive dietary iron intake was reduced. The degree of anaemia can often be gauged clinically with accuracy but when the piglet is suffering from other diseases it is easy to be misled. However, when the diagnosis depends on a simple estimation on a small volume of blood there would appear to be little reason for doubt. Yet one is commonly asked to examine herds in which the piglets are said to suffer an anaemia that does not respond to treatment. Although there are cases of this type they are generally affected with another intercurrent disease and by far the most usual reason for the poor response is that the piglets are not, in fact, anaemic. Thus the diagnosis of anaemia in the field is often based on signs, particularly enteritis, that are not necessarily related to anaemia, and the position is made more confused by the fact that both nutritional anaemia and several of the other conditions that cause enteritis improve rapidly once the piglets are given access to pasture.

Rhinitis

There is among suckling pigs in Britain an infective rhinitis characterised by inclusion bodies in the nasal mucous membrane (Done, 1955) and, in keeping with the findings of Done, we have observed this entity progress to a chronic condition with distortion of the nose. It has been stressed by Kerruish (1956) that some degree of nasal abnormality is very common among adult pigs and that the condition is probably worse in the Landrace breed because the hard structures are more susceptible to distortion. Much work needs to be done on the aetiology of atrophic rhinitis in pigs but there is also a great need for information on the effect of the primary infection. Thus although we have studied outbreaks of "inclusion-body" rhinitis in Landrace and non-Landrace pigs in which the piglets were obviously ill and breathing with difficulty, such a degree of affection appears to be unusual. If much of the damage in adults originates from " inclusion-body " rhinitis it would seem that in most piglets the primary infection passes unnoticed. Perhaps it is the secondary organisms that are important or the extent to which other tissues such as the lower respiratory tract might be affected simultaneously. Questions such as these are far from being of academic interest, because one is constantly faced with the decision on the extent to which different diseases might check the growth of suckling pigs. Reference is made to this problem again but without information on the relative importance of enzootic pneumonia, infective rhinitis and other possibly widespread diseases it is difficult to advise pig-farmers on the economic merits and possible benefits of different isolation and eradication policies. There is also the resistance of the host to be considered but if disease-free pigs were available for studies of this type they could be kept under different systems of management and housing during infection.

Pericarditis

This condition is one that we see frequently and it has occurred for some years in piglets at grass in our own herd. The piglet, often in good condition and not anaemic, usually dies suddenly at about 2 to 3 weeks of age and generally only one or two pigs succumb in a litter. The most characteristic *post-mortem* finding is a great deal of pericardial fluid sometimes containing fibrin. The pericarditis is often accompanied by fibrinous peritonitis. Bacteria may be recovered from many sites in pure culture, but they vary from pig to pig and more commonly routine bacteriological tests are negative. A very similar syndrome has been seen shortly after birth, taking a more severe form and sometimes destroying most of the

litter. We have tried several transmission experiments with litters of very young pigs without success and the facts available at present are too vague to relate the disease (or disease complex) to any other entity in the literature such as that reported by Shanks (1953).

Enteritis

Enteritis is now one of the commonest reasons for seeking advice in this area. The problem is presented in various ways. Sometimes the diarrhoea starts soon after birth but most commonly it arises at about 2 to 3 weeks, while it may often start at the older age and then occur in younger pigs. The diarrhoea may produce only a temporary check in growth so that the problem is one of a fairly low-grade economic loss but at other times it ushers in a number of syndromes that leave many of the pigs severely stunted. There are some forms of enteritis that rapidly respond to antibiotic treatment and others that occur spasmodically in litters; these are not a problem. The types of enteritis now under discussion are those that occur on a herd basis and often defy a whole variety of antibiotics.

It is useful at this point to consider the main possible causes of enteritis because the problem is particularly complex. Enteritis may occur solely from a dietary cause and this is seen well when piglets are being artificially reared and suddenly start to overeat. Removing the food trough for 12 hours or so will often arrest the condition but it is possible that from such simple beginnings more permanent trouble arises. Secondly, there might be a number of causes that attack the intestine specifically but it is doubtful whether such causes account for the bulk of the troublesome enteritis to-day. In the writer's view attention should be focused less on the gut both for diagnosis or for treatment, because enteritis may be secondary to a primary cause. The primary cause may be generalised under the heading of lowered resistance or it may be more closely related to a specific disease. Thus an example of the former general cause is nutritional anaemia, where presumably intestinal bacteria normally kept under control are able to affect the weakened pig. It is interesting to note under this heading that although the enteritis would be common to many pigs it would not usually transmit from one animal to another; that is, a general nutritional cause predisposes to a widespread individual enteritis and it is possible to house healthy pigs with the affected pigs without the disease spreading.

When the enteritis is related to a specific disease, however, we have a completely different set of conditions, because it is not so much that the enteritis is infectious but that the primary cause is readily transmissible. Thus enteritis is a common sign in young animals when they are first infected with a number of diseases; witness the enteritis of calves infected with virus pneumonia. A good example of this type of enteritis is seen in swine fever, of which we have recently seen many cases that might have under different circumstances passed undiagnosed, because they were in litters suckling immunised sows. Again, in a litter of pigs that later developed poliomyelitis, the earliest sign of the disease was enteritis uncomplicated with neurological signs. Some of the most severe enteritis seen by the writer on a herd basis was in a large herd where pig pox was passing through the litters in a very severe form. There is no shortage of examples of this type, although it might be argued that poliomyelitis, swine fever and pig pox are not widespread among piglets. With diseases like poliomyelitis, however, the disease unaccompanied by marked neurological signs might be not uncommon and there are certainly other diseases such as enzootic pneumonia and rhinitis that are very common. Repeatedly, one finds enteritis a problem in herds where pneumonia and rhinitis are also obvious. It is possible that the respiratory and the enteric syndromes are unrelated and are both favoured by a common environment, but is it not also probable that as the litters first become infected after birth they suffer from enteritis? Whether the latter becomes a serious problem or not in a herd is likely to be governed by all the factors that determine whether the pneumonia will be serious, particularly the effect of secondary bacteria. A chain of events is initiated which under good conditions may soon be arrested, but so often they are not and trouble mounts upon trouble until we see the very characteristic stunted young store still affected with enteritis, together with purulent pneumonia, rhinitis, not uncommonly peritonitis and sometimes arthritis. Clearly there is much work to be done in this field but it will often be more profitable to look elsewhere in the pig for the cause of enteritis than in the intestine.

There is little that is common to the above diseases but in concluding this account there are two points that can be stressed. The first is that it is the insidious rather than the dramatic diseases of the piglet that take the greatest toll. The essence of good pig-keeping is to achieve high birth weights, followed by a smooth, uninterrupted, rapid rate of growth and the time is ripe to look more closely into the burdens imposed by these sublethal and subclinical conditions so that their economic effects can be evaluated more precisely. The second question is one of some magnitude—husbandry. Some diseases can only be insured against but there are many where husbandry can make all the difference. There is a danger that in the age of antibiotics too much emphasis can be given to therapy; it is often simpler to create conditions to prevent unthriftiness than to cure it in suckling pigs and in many of these herd problems the sums spent on therapy before the root of the trouble is sought may be excessive. Farming is changing as rapidly as veterinary science and some farmers are seeking very high standards. Our advice is being sought increasingly because pigs are not growing fast enough rather than because they are dying. We are presented with figures for average weaning weights, conversion ratios and average times to bacon weight and asked to improve upon them. To meet this very commendable challenge of the farmer, knowledge on the host-parasite relationship of the subhealthy pig is all-important.

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THE SPEAKER'S INTRODUCTION

Dr. Goodwin said that he was grateful for the opportunity to present a paper on the ills of young pigs. The subject was economically of some concern, and he was acutely aware of the extent of the problem in the field because he had almost reached the point of being totally submerged by specimens, queries and advisory visits in connexion with farms where many of the young pigs were sick or dying. He emphasised that some of his observations derived from joint work with Mr. Jennings.

The relationship between the young pigs and the sow was particularly close, and it was impossible to move among the diseases of baby pigs without getting very much involved in the problem of agalactia. He had said nothing of this very thorny problem in his paper, but he wished to mention, in confirmation of the remarks previously made by Dr. Cross that they had recently started some work on this condition and it augured well. The first results had been encouraging and he hoped they would have something significant to offer before long.

The condition that he had called pericarditis often revealed considerable liver damage, and in some of the cases he had seen recently the liver was damaged to an extraordinary degree. Mr. Jennings was studying a disease some years ago, which he had called hepatitis of sucking pigs, and the author felt that that condition and the one he had mentioned were probably the same. It was likely that they had merely singled out different striking *post-mortem* lesions in the same syndrome.

With regard to the question of diarrhoea in piglets, he did not wish to leave the impression that he had no belief in specific enteric factors; but in visiting farms where there was a problem of diarrhoea he commonly found that the practitioner had concentrated on specific therapy and had not looked far beyond the diarrhoea itself. Furthermore, he received claims that such and such a product was the answer to scours in piglets. The answer to enteritis in piglets, as in calves, lay far more in environmental and other questions, and he had consequently emphasised that point of view.

Dr. Goodwin concluded his remarks by showing a series of colour slides depicting liver damage and other effects on piglets of vitamin A deficiency; the various skin discolorations seen in haemolytic disease; his rapid slide-test for the latter condition; and *Clostridium welchii* infection in newborn pigs.

The Opener

Mr. H. I. Field, in opening the discussion, congratulated Dr. Goodwin both on his paper and on choosing to devote his time and energies to a study of problems in young pigs.

This was a field which, for one reason or another, had previously attracted too few workers, and Dr. Goodwin could at least be satisfied that it was one in which there was ample scope for inquiry.

For some years the pig industry had been second only in importance to milk production in the livestock economy of British agriculture. Its potential was nevertheless severely limited by wastage from mortality and morbidity. Two recent surveys, one carried out by Gracey and his colleagues in Northern Ireland and the other by the Investigation Service in England and Wales, showed that the biggest loss in terms of mortality occurred in the pre-weaning stage. Thus Gracey reported a pre-weaning mortality rate of 18.2 per cent. compared with a post-weaning mortality of only 1.3 per cent., while the Investigation Service survey showed a death rate of 25.4 per cent. during the suckling period.

These percentages in themselves might convey very little, but when they were translated into numbers of pigs involved and cost to the industry the extent of the problem was more readily appreciated. From a simple calculation based on the Investigation Service survey, it was estimated that nearly 2½ million piglets died in England and Wales during 1955, representing a direct loss to the pig industry of £7 million and a 15 per cent. loss in potential turnover, that is around £27 million. These losses took no account of stillbirths, which accounted for another 4 to 5 per cent. of all piglets born. The results obtained in these surveys were supported by the National Pig Records, which for the year October 1954 to September 1955 inclusive, showed a pre-weaning mortality rate of 20.3 per cent. These were the facts.

If it were true, as Dr. Goodwin had said, that the insidious rather than the dramatic diseases of the piglet took the greatest toll, then losses from mortality, morbidity and lack of thriving combined must be at a higher level in pigs, related to total production, than for any other species of farm livestock. Yet despite the important position which the industry occupied in the livestock economy of British agriculture and the enormity of the losses which it experienced, the amount of money and effort devoted to a study of its problems was less than that given to branches of livestock of lesser economic importance. Any advance in knowledge had been due mainly to the efforts of individuals rather than to a concerted effort of the kind that seemed to be necessary.

Surveys into wastage and disease served an important purpose in showing where one's energies should be directed, particularly if they were linked with laboratory examination of carcases. This was done in the case of the Investigation Service survey, and as a result there were certain leads which could be followed in future studies. It was clear that diseases of known aetiology were a relatively unimportant cause of mortality in young piglets and that the death rate was higher during the winter than in summer. This pointed to management as at least one of the main factors concerned. The causes were undoubtedly often ill-defined and overlapping, and a critical appraisal of all factors operating in a given pig unit was usually necessary before progress was made in reducing losses.

Dr. Goodwin had described his interesting work on 4 conditions that occurred in baby pigs. The speaker found it difficult to follow his argument in deprecating the use of the term "baby pig disease." This term had originally been used by Graham and his colleagues to describe a clinical entity in baby piglets and was so used in this country by those engaged in the investigation and diagnosis of pig diseases. This clinical entity, as originally defined, appeared to be clear-cut and not likely to be confused with any other known disease of the new-born piglet. Hence the term had a specific meaning. It was when the term hypoglycaemia was used as descriptive of a specific entity that confusion was likely to arise, for Dr. Goodwin's valuable studies had shown that young piglets became hypoglycaemic whenever they were starved of food, and starvation might be due to any one of a variety of causes.

A great deal of space was given in the paper to a consideration of vitamin A deficiency and its relationship to stillbirths, piglets weak at birth and microphthalmia. This might give rise to the erroneous impression that vitamin A deficiency was a common cause of piglet mortality. A colleague of Mr. Field's, Mr. C. N. Saunders, was making a special study of abortion, stillbirths and early post-natal deaths in pigs, and some 40 outbreaks had been investigated this year. Vitamin A estimations were carried out as a routine on foetal livers and, where possible, maternal blood and liver. In only one outbreak had the problem been found to be associated with low vitamin A levels. This outbreak involved 11 gilts, all of which farrowed stillborn or weakly piglets. Vitamin A estimations were made on the livers of 18 piglets; none was detectable in 13, and in the others the levels ranged from 1.5 to 3 international units per gramme. Yet the piglets were all of normal size and showed no signs of microphthalmia. On the other hand, a case had been seen in which piglets born with skeletal abnormalities, anophthalmia or microphthalmia came from a herd with a normal vitamin A status.

The same danger of over-emphasis applied also to trembling and haemolytic disease. Piglets affected with these diseases represented less than 2.5 per cent. of the 1,500 piglets submitted for examination to investigation centres during 1955. That was felt to be a fair indication of the relative incidence of these diseases as causes of piglet mortality throughout the country. It was true, as Dr. Goodwin had indicated, that in some herds these conditions might assume serious proportions, but the over-all loss to the pig industry was comparatively slight.

The detailed studies of Dr. Goodwin and his colleagues on haemolytic disease had nevertheless been particularly valuable in showing the potential danger of certain methods of vaccine production, and the work had shown further that by selection of breed for vaccine production, this potential danger could be largely avoided.

The author had discussed 4 problems which, in his view, warranted clinical comment at the moment. Two of these conditions, anaemia and enteritis, had been problems for a long time. Dr. Goodwin had stated that in his experience nutritional anaemia was now comparatively uncommon in the field. There was certainly a sharp fall in its incidence during the winter of 1956-7, but it was probable that this was a seasonal variation related to the mild weather conditions. Despite the fact that iron was widely used as a prophylactic and therapeutically, the fact remained that some 15 per cent. of the suckling pigs examined in investigation centres during the 12 months preceding the end of February, 1956 were affected with this disease. One would support his plea for the need to confirm clinical diagnosis of anaemia by blood examination, and would agree with him on the importance of enteritis as a cause of mortality, morbidity and lack of thriving in pigs in both pre- and post-weaning periods. The experience of Mr. Field and of his colleagues, based on a detailed field study of outbreaks, was that although some outbreaks were nutritional in origin and a few symptomatic of specific disease, the epidemiological evidence in others had all the features of a localised bowel infection which was transmissible.

Dealing with the two remaining conditions to which Dr. Goodwin had referred—rhinitis and pericarditis—Mr. Field said that the former was being studied by his colleagues at Weybridge, both experimentally and from the field, and it seemed probable that the answers to some of the questions posed by Dr. Goodwin would be available shortly. It would be both premature and unprofitable to debate the problem further until these studies were completed.

The speaker said he was surprised to find that Dr. Goodwin considered pericarditis to be sufficiently common to warrant discussion. One felt that his material must be very selective or that there must be something very abnormal about his departmental herd if he found the condition to be of frequent occurrence. It was accepted that such cases did occur, but they represented a minute proportion of the morbid material examined in diagnostic laboratories.

Some progress had been made during the last few years towards a better understanding of the problems of the effects of sub-lethal and sub-clinical conditions which, together with husbandry, Dr. Goodwin regarded as the factors which mainly influenced the economics of pig farming. But a great deal of work remained still to be done. Surveys could be made to indicate the extent of the problem. One could apportion the mortality and morbidity amongst cer-

tain clinical entities or ascribe it to inferior husbandry; but unless these entities, together with the effects of variation in husbandry, could be studied intensively, it would be a long time before one would be in a position to give the sort of advice which Dr. Goodwin had said he was asked for by progressive farmers. Mr. Field gave it as his opinion that this stage would not be reached until the amount of research devoted to the problems of the pig industry bore a closer relationship to the position which it occupied in the livestock economy of British agriculture.

The General Discussion

Mr. A. R. Jennings (Cambridge): "I should like to amplify the remarks made by my colleague Dr. Goodwin on the subject of pericarditis. We first saw cases of this syndrome about 3 years ago. The usual clinical history was of sudden death, one or two piglets in a litter would be found dead without any premonitory signs. Sometimes there was a history of respiratory embarrassment. These piglets were not anaemic. On *post-mortem* examination there was often a very striking liver change. The liver was grossly enlarged and covered with fibrin. The surface of the liver was mottled and this was very obious on incising the organ. In association with the liver lesion there was invariably a fibrinous pericarditis. Some cases exhibited a fibrinous pleuritis. Histologically the liver showed extensive necrosis. Essentially the necrosis was centrilobular in distribution and in some areas many lobules were completely necrosed. Eosinophilic structures were noted in the cytoplasm of a few liver cells but it has since been demonstrated that these inclusions are not specific for this condition. The lobular distribution of the necrosis was patchy and irregular. Pigs from affected litters which survived to bacon weight showed very extensive fibrosis at slaughter. In some of these cases there was very gross cirrhosis and the liver was much enlarged and hobnailed in appearance."

Mr. R. A. Huck (Weybridge): "May I make a small contribution to Dr. Goodwin's excellent paper? We have experienced the phenomenon of the birth of abnormal piglets at term following the experimental infection of pregnant sows with virulent swine fever virus. From abnormal piglets born on a farm where swine fever was reconfirmed after such births, we have recovered virulent swine fever virus.

"With regard to Mr. Done's statement that the phenomenon of the birth of abnormal piglets, may occur when sows are infected with a mild virus, during the first 30 days of pregnancy, we have found in the course of a field trial with lapinised swine fever vaccine this phenomenon was manifest in some cases where sows were vaccinated up to 60 days after service."

Dr. J. C. Buxton (Liverpool): "I am particularly interested in the pictures which Dr. Goodwin showed to us of pigmentation in piglets affected with haemolytic disease. It is, of course, the typical as well as the most easily discernible symptom of this acute disease. In the early cases we found, in some animals, marked pigmentation of brain tissues, resembling kernicterus of rhesus children. Bile pigments are known to be very damaging to brain tissue in humans, resulting often in mental deficiency and varying kinds of muscular paralysis. Those constitutes delayed symptoms of the disease and I wonder if Dr. Goodwin has been able to observe such manifestations in his experimental pigs? A further question on the same matter arose when Brooksbank suggested 3 years ago that trembling in piglets might be connected with the presence of a virus, possibly that of swine fever, in the central nervous system. The connexion between swine fever vaccine and haemolytic disease is now well known and it is interesting to speculate on the possibility of another side effect.

"I was interested also in Dr. Goodwin's pictures portraying generalised oedema in cases of hypovitaminosis A. We have produced an exactly similar condition in lambs by subjecting gestating ewes to vitamin A deficient diets; and hydrocephalus, with varying degrees of brain cavitation, are now known to be associated with vitamin A deficiency in the young, resulting in hind-quarter paralysis. It seems to be possible, therefore, that the paralysis which Dr. Goodwin observed might have resulted from cavitation of the lateral ventricles."

The Reply

Dr. Goodwin, replying to the discussion, congratulated Mr. Field for opening the discussion so well and particularly for stressing the economic importance of piglet morbidity to the pig industry in general. It was obvious that he and Mr. Field had not consulted together, because he had to disagree with Mr. Field on the question of baby pig disease and hypoglycaemia; the latter could not be a specific entity.

He was not attempting to evaluate the economic importance of these different diseases, and did not wish to give the impression that one was more important than the other. He merely wanted to give a certain amount of new knowledge as factually as possible.

Dr. Goodwin said that he would be the last person to over-emphasise the economic importance of haemolytic disease, and he had tried to ascertain its place in the whole complex problem of mortality after birth. It was, however, much more common than many believed it to be.

As far as trembling was concerned, he was changing his opinion. He would not agree that it was a rare disease. He had recently carried out a survey of blood groups among various breeds of pigs, in the course of which he had visited the farms of many leading breeders. Often an owner would say that the disease had not occurred on his farm, but a few litters would be found suffering from the disease. This, he thought, was a quite common situation. Many breeders did not like to admit it, however, as some people believed the condition to be genetical.

The author referred to the doubt expressed by Mr. Done that a three-week-old piglet, referred to by the author, suffered from vitamin A deficiency. The condition had occurred in a herd where piglets were dying after birth, and it disappeared when the diet was corrected. Secondly, it was similar to a condition shown in pictures published in 1945 by Nordfeldt, in which the disease was produced experimentally. Thirdly, the pathology was quite different from that in the condition of poliomyelitis described by Bendixen and others. He had not referred to paralysis in the new-born pig; the poliomyelitis condition was found in the older pig and this could easily be confused with the paralysis produced by a lack of vitamin A. On the other hand, he had seen the condition known as splayed leg, particularly in the Landrace, and some breeders tied the legs with string. He felt that when one had a breed whose legs had to be tied with string one was getting a little too close in the breeding.

Dealing with haemolytic disease, Dr. Goodwin said that sows seemed to fall into two groups. The antibody either stayed up for many months or it fell fairly rapidly after vaccination. One could try to remate an affected sow with another boar and occasionally there were alternative boars that would not be incompatible with the sow. He could not understand why Mr. Parker had had difficulty with the slide test. It had been used successfully in the Veterinary Investigation Laboratory at Cambridge and it had been found to be very sensitive.

He did not subscribe to the view that there were any after-effects of haemolytic disease. While admitting that he might be wrong, he had not been able to demonstrate any such effects. In his opinion, if the piglet could survive for one week, no ill-effects were suffered. The crisis occurred in the first 5 days but if the piglet survived beyond this time it showed an extraordinary ability to regenerate its blood.

On the question of scours, Dr. Goodwin said that he had gone out of his way to play down the question of *Bact. coli* as a prime factor. He did not think the real answer to calf scours in the field lay so much with *coli* as with the various predisposing conditions, and the same applied to piglets.

Present-day Problems in Veterinary Therapeutics

BY

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IN the preparation of a paper dealing with the subject of present-day problems in veterinary therapeutics the author has a choice of methods in dealing with the subject. He may describe a number of instances that have come to his knowledge and so, as it were, present a catalogue containing at least some of the problems. He may, on the other hand, discuss the fundamental difficulties that lead to these problems occurring in veterinary practice. It would seem that possibly the most effective course would be to combine these two methods, outlining the fundamental difficulties and then describing specific instances to illustrate the points; it is this method that has been adopted in the presentation of the subject matter of this paper.

Probably no one will dispute the contention that the greatest problem the present-day practitioner has to contend with in veterinary therapeutics is the vast number of new remedies that are being put on the market. This is the result of work on production of new substances by the research staffs of manufacturing chemists. It cannot be denied that in the field of veterinary therapeutics British firms have been well to the fore and that many of their products have resulted in a great surge forward in methods of treating animal disease.

The difficulty that the practitioner encounters is to assess the worth of new remedies brought to his notice by one or other of the mediums of advertising or publicising such products.

In comparison with the veterinary practitioner the bacteriologist is fortunate for he has Koch's postulates to guide him as to the veracity of claims made. Because of the absence of any such therapeutic postulates the practitioner has no yardstick to apply to the claims made for a new remedy. Even if such a yardstick existed, the information supplied in relation to new remedies would often be insufficient to enable the practitioner to use his yardstick. There are, of course, firms who consistently make a practice of furnishing very full information as to their products, but this is unfortunately neither a uniform nor a common practice.

This lack of adequate details naturally leads to an attempt to define the type of information that should be supplied when a new remedy is placed on the market.

It is suggested that the information furnished should include at least the following:—

1. *Pharmacological Basis*

A statement of the pharmacological grounds on which a hypothesis was advanced that the substance in question might possess therapeutic value. This statement should contain a brief description of the work on which the contentions as to possible therapeutic value are based.

2. *Therapeutic Tests*

A statement of the therapeutic trials conducted to establish that there was substance in the conception of therapeutic value based on the pharmacological evidence supplied. This statement should include adequate details of the extent of the therapeutic trials, including such essentials as the species and number of animals involved. It should be clearly indicated whether the trials have been replicated so that a judgment can be formed as to the possibility of good results claimed being merely a chance happening turning up in a single small trial.

3. *Toxicity Trials*

The statement of toxicity trials should clearly indicate whether the toxicity trials have been confined to small laboratory animals or whether after a preliminary screening for toxicity with small laboratory animals the trials have been extended to include domesticated animals; if so, what species were involved, and how many animals were used. It should also be made abundantly clear whether these toxicity trials were tests of acute toxicity only or whether chronic toxicity tests were made. It should also be indicated whether the trials were sufficiently extended to exclude delayed effects. Finally such things as the size of dose, route, frequency and time period of administration should all be clearly stated.

It may be said by some that these requirements are far too stringent, but against that there is surely the unassailable fact that no one has any right to use a drug in the treatment of animal disease unless he has at least the information asked for in these requirements. Anyone who has been in practice for more than the very briefest of time must be familiar with drugs which were introduced with a great flourish and after a period of apparent favour were found wanting and were discarded. In some of these cases the information supplied as to the pharmacology of the substance was quite inadequate if not actually non-existent. A recent example is the large number of drugs that have been rushed into the market under the new name for a type of sedative—to wit "tranquillisers." What is the mode of action of some of these? The literature accompanying some of the products gives precisely no information.

In other instances therapeutic claims for a particular substance have not been borne out by clinical experience and then, with the remarkable property

of "hindsight," it is realised that the claims were founded on the flimsiest of grounds. An example of this is to be found in so-called colloidal manganese and manganese butyrate which are probably never used nowadays and thesubstance known as S.U.P. 36.

It is perhaps in regard to toxicity that the practitioner is most often let down. The therapeutic index has been called the factor of safety and is the ratio of the toxic dose to the therapeutic dose. Usually the tests have been carried out on small laboratory animals and the results are only applicable to domesticated animals when it is known that a strictly comparable substance with the same therapeutic index has been found free from toxicity. In the case of a new substance the therapeutic index computed on small laboratory animals may fail as a guide to the safety of the product when used on domesticated animals. Trials conducted on domesticated animals are necessarily expensive and tend to be too often confined to a limited number of observations on a small number of animals. Very often these observations are found to have been limited to short-time immediate reactions. Toxic reactions may be immediate, but they may be delayed even when only one dose has been administered. On the other hand, toxic effects may only become evident after repeated dosage and that may mean either continuous dosage or dosage at longer and possibly irregular intervals. Then there is the problem that if the toxic reactions are the results of variations in individual susceptibility, the drug must be used on a large number of animals before any assumption can be made that it is in fact safe. If, as often happens, the preliminary trials have revealed no untoward effects, an undue sense of safety is engendered and when cases of toxicity arise it may not at first be appreciated that the drug concerned has in fact quite a serious toxic risk. This later appreciation of toxicity may make it very difficult—if not impossible—to convince the manufacturer that his product, hitherto considered free from toxicity, is responsible for the illness and death of animals. Gaddum (1953) states that "toxicity tests have often been neglected in the past and the toxic effects of drugs have gradually come to light as the result of their sale to the public."

It is of remarkably little help to the practitioner to find that the contra-indications for a particular drug are stated in vague terms such as renal and hepatic damage and any evidence of circulatory weakness. Pious platitudes of this kind may provide a way out from blame in respect of a product, but how the clinician is expected to assess on such platitudes the relative safety of the product on a sick animal is beyond comprehension. There is only one safe course and that is to avoid using the product until more adventurous spirits have proved its safety.

In a leading article entitled, "New Drugs, Old Dangers," *The Lancet* (1957) made the following important statement:—

> "Manufacturers are anxious to bring forward their more promising products without delay. Many manufacturers take great pains to secure evidence of freedom from toxicity; others have less exacting standards. But whatever may or may not have been done before a drug is offered for general use the surest safeguard is to look on every newcomer as potentially dangerous, and to be sceptical of confident statements to the contrary—for the first five years at any rate."

Two examples will suffice to illustrate these points in regard to toxicity, namely, Betanaphthoxyethanol and Phenothiazine.

Betanaphthoxyethanol was introduced as an intravenous anaesthetic for horses. At first it appeared to be safe in use but when its use was extended to a larger number of horses it was found to be toxic to a small but not insignificant proportion. Death usually took place as a result of acute pulmonary oedema. There is no known method of determining which horse may be the victim of acute pulmonary oedema following intravenous injection of the drug. In effect this has meant a radical revision of the recommendations in regard to the use of this intravenous anaesthetic, which now virtually exclude its use in horses. The *British Veterinary Codex* 1953 says, "Reports on the value of Betanaphthoxyethanol and on its after-effects are conflicting and it should be used with caution."

Phenothiazine when first introduced was used on a large scale as an anthelmintic in horses and for a time it appeared that any toxic actions could be disregarded. Then it was realised that in young horses, and especially in young thoroughbreds, the number of fatal cases of toxicity was sufficient to justify some modification of the view that it was an entirely safe remedy. Another point, only realised after years of experience, was that the selective action of the drug could permit species, hitherto regarded as non-pathogenic, to assume when left unopposed a quite serious pathogenic role.

Reference to medical literature shows how two substances—both tranquillisers—said to be quite innocuous have now been shown to have quite undesirable side-actions. The toxic effects of meprobomate received attention in an editorial in the *British Medical Journal* (1956). Marley & Chambers (1956) drew attention to the toxic effects and side-effects of methylpentynol. There is the classical example of amidopyrine. This drug was used as an antipyretic and analgesic. The long-term toxic actions were not realised for years and were only fully appreciated after a careful statistical inquiry had been made as to the fate of patients who had been treated with amidopyrine. This revealed that in two years 128 cases of agranulocytosis were apparently the result of treatment with amidopyridine and of these 70 proved fatal.

It is perhaps appropriate to refer here to the type of claims put forward in support of a new drug. It is sufficient to quote only two instances both of which might be said to fall into the category of unethical advertising. Both happen to be antibiotic compounds.

In the first instance, claims for a new antibiotic product were supported by a list of allegedly successful cases. The first case on the list was one of a dog which had been diagnosed as suffering from an osteosarcoma of the distal end of the radius and ulna. Amputation was carried out through the middle of the humerus. The antibiotic product was adminis-

tered daily and "first intention healing resulted." In the circumstances it would be a very poor surgical craftsman who could not secure first intention healing without resorting to an antibiotic umbrella. The only thing the case quoted did prove was that in the particular case the antibiotic product was innocuous.

In the other instance it was claimed that a new antibiotic product was successful in clearing up a case of cystitis in a dog. In the first place no indication was given of the type of cystitis and its possible relation to prolonged retention of urine. There was no mention of a bacteriological examination of the urine. Many of these cases in dogs are associated with gram-negative organisms. The antibiotic concerned, however, acts only on gram-positive organisms. So this case history completely failed to establish anything in regard to the antibiotic product concerned.

The problems presented by the introduction of new remedies could to some extent be resolved by a system of presenting adequate information as to the product on lines such as those outlined earlier. Resolution of these problems would be to the mutual advantage of both manufacturer and veterinary surgeon. Furthermore, if the basic requirements as to information were fulfilled there would be a sound basis for field therapeutic trials that would show up those points that do not as a rule declare themselves in experimental work. Very often the experimental population is not sufficiently representative and is not subject to the diverse and varying influences that affect animals in their natural surroundings. It follows then that relatively restricted experimental trials may fail to reveal the existence of some factor that greatly increases the susceptibility of a particular species of animal to the drug concerned.

Field therapeutic trials will be valueless without the presence of controls. This necessitates some means of overcoming the all or none attitude of owners to the application of treatment to a group of animals. Such trials to be effective must embrace sufficiently large and sufficiently widespread groups of animals to exclude the possibility of satisfactory results being fortuitous. All this points to the need for properly planned organisation and for sufficient finance to enable field therapeutic trials so to be carried out that they may provide reliable information. It is to be hoped that the efforts of the British Veterinary Association in this direction will prove successful.

It is useful now to turn to some of the more specific problems that are encountered in present-day veterinary therapeutics.

Choice of Antibiotics

Following on the introduction of penicillin and streptomycin to veterinary therapeutics there has been a veritable flood of newer antibiotics. The practitioner is then faced with the problem of deciding which antibiotic to use and in the case of penicillin which preparation to use. This problem can best be discussed by reviewing the merits of the various compounds.

Penicillin

Penicillin has been found to be effective against most of the cocci and against gram-positive organisms causing animal diseases. There is a choice of preparation.

Benzylpenicillin is supplied as either the sodium or the potassium salt; it is usually referred to as crystalline penicillin. Parenteral injection of a sufficient dose promptly produces adequate blood levels. This is the form with which treatment should be initiated in acute infections endangering life. The proportion of crystalline penicillin absorbed when given by mouth varies very greatly.

Procaine penicillin is relatively insoluble and absorption is delayed so that a single adequate daily parenteral injection will produce a bacteriostatic level lasting for twenty-four hours. Development of a bacteriostatic level with procaine penicillin is less rapid than with benzylpenicillin.

Benzathine penicillin is a relatively insoluble derivative of penicillin. When given intramuscularly it produces very prolonged but rather low blood levels. The evidence as to its value when given orally does not strongly suggest that it is in any way superior to crystalline penicillin.

Phenoxymethyl penicillin which has been termed "Penicillin V" is relatively stable and appears to be resistant to an acid medium. It can be given orally and then in dogs and cats produces a higher blood level than other forms of penicillin given by mouth. It is doubtful if in the larger domesticated animals adequate blood levels would be produced by the oral administration of this compound. In any case oral administration might be more troublesome than the parenteral injection of procaine penicillin. The relative costs of the two products would require to be considered. The chief use of phenoxymethyl penicillin would appear to be in small-animal practice where it is desired that treatment should be continued by the owner. It is necessary to give the product every four hours to maintain an adequate concentration and this may prove more troublesome than a daily injection of procaine pencillin.

A useful method of dealing with an acute infection is an initial injection of crystalline penicillin combined with procaine penicillin followed by daily injections of procaine penicillin.

Streptomycin

Streptomycin is slightly less effective than penicillin against most cocci causing animal disease. It is, however, effective against the gram-negative organisms of veterinary significance.

In some acute infections the clinician is presented with the problem that the clinical condition he has encountered could be caused by either a gram-positive or a gram-negative organism. He cannot always in these cases obtain suitable material to send to a laboratory for bacteriological examination and even when he can there must be a delay while the organism is typed. The case, however, requires immediate treatment, and in the circumstances it seems a perfectly justifiable procedure to use both penicillin and streptomycin. It is perhaps only in such circumstances that the use of an "antibiotic umbrella" is justified.

Chloramphenicol

Chloramphenicol can cause various blood dyscrasias including agranulocytosis and a fatal aplastic anaemia. Though it has a wide antibacterial action this disadvantage of toxicity coupled with its cost virtually rules out its regular use. Intramuscular injections in the dog at any rate are to be avoided on account of the pain they cause.

The toxic effects mentioned are not produced by normal topical applications and its value in the treatment of foot-rot in sheep and comparable conditions in other animals is well known. Its use in the treatment of infections of the external ear in the dog has the same disadvantage as any other antibiotic that if the bacterial flora are wiped out an intransigent fungal infection may result.

Tetracyclines

The tetracyclines can be regarded as a group; they are chlortetracycline (Aureomycin), oxytetracycline (Terramycin), and tetracycline (Tetracycline or Achromycin). They are all antibiotics with a wide range of antibacterial activity which may be regarded as being virtually common to all. They are effective against a wide group of gram-positive and gram-negative bacteria. They are also effective against rickettsiae and a few of the larger viruses.

Their indiscriminate use should be discouraged and their use as a primary remedy cannot be justified in part on account of the expense involved. They should not be given by mouth to ruminants above the age when they are dependent on milk. The tetracyclines should be retained as a means of treating infections that have not responded to treatment with penicillin and streptomycin or to sulphonamides.

The strong light that of recent years has shone on the antibiotics has left the sulphonamides in the shade. For acute respiratory infections in cattle and sheep sulphadimidine is preferable to penicillin alone and possibly preferable to the combination of penicillin and streptomycin.

Antibiotic Resistance

There does not as yet seem to be a convincing volume of evidence suggestive of antibiotic resistance developed as a result of antibiotic treatment of sick animals. There is, however, some evidence that tends to suggest in subacute infections larger doses, more frequent administration and a larger course of treatment with penicillin is necessary.

On the other hand there is a strong body of opinion amongst practitioners that where young pigs are provided with a diet containing antibiotic supplements, particularly the tetracyclines, outbreaks of diarrhoea occur that prove completely resistant to any known antibiotic. These outbreaks were unknown in these herds before the antibiotic supplemented diet was used and did not develop in new lots of pigs fed on a diet without the antibiotic supplement.

Smith & Crabb (1957) provided some most valuable observations on this important problem. They appear to show that the feeding of a tetracycline supplement diet stamps out the tetracycline-sensitive organisms and leaves the tetracycline resistant organisms with an undisputed field. They point out that in pigs the change that occurred after tetracycline feeding was "from a predominantly sensitive to a predominantly resistant *Bact. coli* faecal flora."

Antibiotic Hazards

Reports of untoward results following the intramuscular injection of antibiotics in animals appear as yet to be very scanty.

Three somewhat similar episodes have been observed in horses following the intramuscular injection of penicillin. In each case the horse had received a punctured wound which was showing evidence of infection. In one case the wound was just below the elbow, in one in the region of the carpus and in the third midway between the elbow and carpus. In each case shortly after the injection the horse showed signs of distress and within a few hours there developed an extensive intensely painful swelling around the wound. In one case brought to my notice this phenomenon was repeated when the horse received an injection of crystalline penicillin the following day. Study of these cases leaves no doubt that the reaction was due to penicillin. It is not possible to say with any certainty that these animals had not previously received penicillin injections. At the time the reactions were distinctly alarming but proved to be more alarming than dangerous. Antihistaminic treatment was used but it is impossible to say what part this treatment played in recovery. At the moment these seem to be rare and unusual cases. The feature common to these cases was the presence of an infected punctured wound with tissue damage.

The position that may develop in pigs following the use of antibiotics by mouth has already been mentioned.

An experience with a three-year-old Alsatian bitch illustrates what may happen with excessive oral antibiotic therapy. This bitch belonged to a member of the medical profession. It developed signs of respiratory trouble that might have been related to broncho-pneumonia. The owner treated it with benzathine penicillin by mouth for three days. The animal was then passing very smelly faeces bright red with blood. It then received chloramphenicol by mouth followed by chlortetracycline by mouth for three days. When first seen it was a dull, listless animal with very rapid respirations and a fast, weak pulse, temperature 102.4° F. There was an area of dullness in the lower part of each side of the chest. Diarrhoea was present but there were no signs of blood in the faeces. Treatment consisted of rest and warmth with a light, semi-fluid diet. In five days the respiratory condition had subsided, but the diarrhoea still persisted. A mixture containing chalk and kaolin was then given three times daily and the diarrhoea ceased in two days. Blood films showed no abnormality other than a monocytosis (monocytes 19 per cent. of white cell count compared with a normal monocyte percentage of 4 ± 3). A second blood sample taken when the animal was clinically normal showed that the monocytosis was subsiding (monocytes 9 per cent. of white cell count).

Though damage to the VIIIth nerve might occur with repeated full doses of streptomycin, it is im-

possible to say that an unequivocal instance has been encountered.

The Use of Drugs Known to be Toxic

A rather interesting problem arises when a drug known to have considerable toxic propensities is advocated as a remedy for a disease or diseases for which there is no known effective treatment. An example of this type of problem is presented by the decision necessary if the drug phenylbutazone is to be used. Phenylbutazone is chemically related to amidopyrine. It has been advocated as a substance suitable for the treatment of rheumatoid arthritis and anchylosing spondylitis, principally in dogs. Robson & Keele (1956) point out that in respect of human subjects phenylbutazone is in no sense curative in rheumatoid arthritis, and symptoms recur as soon as the drug is eliminated from the body. The mode of action is uncertain; it may act solely as an analgesic or it may influence the tissue processes that cause the inflammation and pain in rheumatoid arthritis. It is, however, a notoriously toxic substance and even the most conservative estimates indicate that toxic symptoms may be expected in one out of four or five human patients receiving the drug for any length of time. It must be one of the most versatile of toxic agents judging by the list of toxic manifestations which include severe gastro-intestinal irritation, skin rashes, fatal jaundice, polyneuritis, agranulocytosis, aplastic anaemia, thrombocytopoenia and oedema to name only a few.

It is difficult, if not impossible, to see how it can be justifiable to prescribe such a notoriously toxic drug, and this difficulty is intensified when it is realised that it is only a palliative and is not curative.

Choice of Treatments in Acetonaemia

It is impossible in the compass of this paper in detail to deal with the many treatments that are available and lauded for the treatment of acetonaemia. The wide diversity of recommended treatments presents a problem for the practitioner, the problem being for him to decide which of these treatments he should adopt in his practice. It is quite clear that the solution is arrived at by a process of trial and error and that the treatment most uniformly successful is adopted as a routine. It then becomes clear that in some districts one treatment is more successful than any of the others, while in other districts it is another treatment that is the more successful. Even if allowance is made for a proportion of cases that undergo spontaneous recovery it is clear that each of these diverse treatments has some merit. If the disease syndrome known as acetonaemia is approached from the viewpoint that it responds to a diversity of treatments the fundamental conception emerges that under the term acetonaemia there are grouped a number of conditions that have the common feature of ketonaemia which in turn is reflected in the ketone content of the milk and urine. The position has really been clarified—not complicated—by the recognition that cows suffering from displacement of the abomasum exhibit a degree of ketosis. If then the principle is accepted that bovine acetonaemia is a group of diseases there opens up a new prospect of investigation towards separating the group into its component parts. Until that is accomplished the only feasible solution of the practitioner's problem, to decide which treatment to use, is that he should determine by trial and error the treatments most appropriate to use in his own area.

Biological Products

Biological products in the form of vaccines, sera and antitoxins are used on a very large scale for the prevention of disease amongst the domesticated animals both in this country and throughout the world. To a somewhat lesser extent biological products are used in the treatment of diseased animals. In general it can be affirmed that the place of biological products is essentially to be found in the realm of prophylaxis rather than in the realm of treatment.

In spite of the vast scale on which standard biological products are used, the amount of trouble experienced following their use is very small. This is a remarkable tribute to the care exercised in developing the method selected and the constant meticulous supervision of the production of the product. It would be wrong to introduce this subject without paying this tribute to those who are responsible for the production of these products.

There is, however, one vaccine with which more trouble seems to be experienced than with any other, indeed, possibly than all the others put together. It is the vaccine used to produce active immunity against pulpy kidney and enterotoxaemia in sheep. The form of untoward occurrence is the development of a violent reaction at the site of inoculation. These occurrences have been reported from a number of areas in both England and Scotland. When they do occur the results can be quite disastrous, thus in one instance where over 300 lambs were involved the mortality rate was 10 per cent. and every lamb showed some reaction at the site of inoculation. In fatal cases the lesion can be described quite simply as one of extensive gangrene.

These episodes are most unfortunate for they bring into disrepute a most useful method of protecting sheep against a disease that may cause quite substantial losses. Not only does the farmer whose stock have suffered refrain from using the vaccine again but very often his neighbours do so too. Then there is the position that arises between the farmer and the veterinary surgeon who advised him to use the vaccine.

A study of several such incidents has brought forth the following interesting points. These incidents have occurred when sheep have been inoculated inside the thigh and when they have been inoculated behind the scapula. They have occurred when the sheep were inoculated in dry weather in pens floored with concrete and in wet weather when the conditions underfoot were very bad. They have occurred on farms where the farmer has inoculated his sheep for a number of years without any trouble and on farms where the farmer has himself inoculated sheep for the first time. Study of the lesions suggested that the lesions seen were the result of a combination of local tissue irritation and the introduction of infection.

Where such trouble has arisen and a veterinary surgeon has inoculated other sheep with the same vaccine using aseptic precautions no trouble has resulted. When the remainder of the vaccine in bottles used by a farmer who has experienced such trouble have been examined by a bacteriologist it has been found to be sterile. But chemical analysis of batches of vaccine have shown them to have a phenol content varying between 0.24 and 0.29 per cent. w/v. These bacteriological investigations have not taken place for at least four days after the vaccine had been used. It is now clear that such a negative bacteriological report does not rule out the possibility of infection having been introduced by the inoculation, but merely indicates that any infection introduced into the vaccine bottle during the process of filling the syringe has been destroyed by the prolonged action of a low concentration of phenol. But short exposure of organisms to the antiseptic in the vaccine would be insufficient to destroy infection introduced at the time of inoculation when using a multi-dose container.

My colleague Mr. Beattie and I were interested to study the local reaction caused by inoculation of vaccine from a bottle, the contents of which were associated with some deaths. Sheep were inoculated at one site with the vaccine and at a corresponding site with normal saline and were slaughtered at intervals and the reactions at the two sites compared. There is no doubt that, while the reaction at the site of vaccine inoculation was substantially more marked than that at the normal saline site, the reaction subsided in the absence of infection. Glenny *et al.* (1931) pointed out that the toxins of the *Cl. welchii* group evoke haemorrhagic or necrotic dermal lesions. Study of some of these episodes in the field strongly suggests that certain batches of vaccine have a greater propensity to cause reaction at the site of inoculation. Examination of a quite small sample of different batches of vaccine has shown a rather striking variation in the *p*H value of the vaccine, thus one batch had a *p*H of 7.1 and another a *p*H of 6.0. It may well be that this variation in *p*H is of significance in regard to the degree of irritation caused at the site of inoculation.

A point that it has not yet been possible to investigate is the effect of storage of the vaccine. The manufacturer presumably keeps the stocks of vaccine in cold storage, but many of these vaccines are handled by distributors and retailers who do not possess cold store facilities. Some circumstantial but inconclusive evidence suggested that one outbreak was associated with vaccine which, though within its expiry date, had been stored at room temperature for a good many months.

As is perhaps to be expected bacteriological examination of the lesions shows a mixed bacterial picture.

Here then is a problem involving two factors, irritation and infection. Under ideal conditions infection can be virtually eliminated, but under field conditions where laymen are doing the inoculations this can hardly be attained. Possibly the standard of cleanliness and methods of handling the vaccine can be raised, but it is difficult to convince a farmer who does other inoculations without trouble that it is not the vaccine that is to blame. It would seem highly desirable that a thorough inquiry should be made into the circumstances in which the vaccine may be more than usually irritant to tissue and if possible steps should then be taken to produce a vaccine of uniformly low irritant character. The B.V.A. Handbook "Diseases of Sheep" mentions fatalities in sheep following inoculations and the advice given there is no doubt appreciated by members of the veterinary profession, but it is doubtful if its existence is known to sheep farmers.

Acknowledgment.—I am indebted to my colleagues for their comments and suggestions during the preparation of the manuscript for this paper.

Summary

The greatest problem the present-day veterinary surgeon has to contend with in veterinary therapeutics is to assess the real value of the vast number of new remedies that are being placed on the market. This leads on to a definition of the type of information that should be supplied when a new remedy is placed on the market.

The information required is discussed under three headings:—

1. Pharmacological basis,
2. Therapeutic tests, and
3. Toxicity trials.

Instances are given of the effect of placing drugs on the market without fulfilling these requirements. Fulfilment of these requirements is an essential basis for properly planned field therapeutic trials.

Detailed consideration is then given to the choice of antibiotics, antibiotic resistance and antibiotic hazards.

The problem of deciding to use drugs of known toxicity is then discussed with particular reference to phenylbutazone.

The difficulty presented by the choice of treatments in acetonaemia is described briefly and the inference drawn that acetonaemia is in fact a group of diseases with one common biochemical feature. The choice of treatment must meantime be governed by determining which is most effective in the district concerned.

Finally reference is made to the problem of untoward reactions at the site of inoculation with vaccines for the protection of sheep against enterotoxaemia. The results of some inquiries into the nature of this problem are discussed.

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THE SPEAKER'S INTRODUCTION

Professor Boddie, introducing his paper, said: "This is the third occasion on which I have presented a paper to the Annual Congress of our Association and I must confess to experiencing some pleasure when I received the invitation to prepare a paper for this Congress.

"I would like to direct your attention to the object of what, in some ways, I regard as the main part of the paper. There seems, to me at any rate, to be a risk of divergence developing between drug manufacturers on the one hand and members of the veterinary profession on the other. That such a divergence should be allowed to develop is not in the best interests of either party. So this section of the paper aims at presenting some of the possible reasons for this incipient divergence and has the aim of showing how further divergence might be prevented.

"I think it desirable to emphasise the importance of the details I have given of the type of information that should be made available to us when new products are submitted to us for trials or are placed on the market.

"After the paper was in print I came across an article in the *New Zealand Veterinary Journal*, by P. B. English entitled "Antibiotics: Their Application in Veterinary Practice." This I found a most useful article putting forward much the same theme as is given in that part of the present paper dealing with antibiotics. It perhaps adds confirmation to what I have said in the paper that the same conclusions should have been formed in regard to antibiotics by those working in the Antipodes.

"The limitations in size necessarily imposed on a Congress paper make it impossible to give full emphasis to all the points raised in the paper. It may be that more emphasis might have been given to the problem presented by the plethora of preparations of penicillin that are on the market. When stripped of their elaborate commercial names and reduced to a statement of the essential penicillin product they contain, the problem becomes simple. I think it will be found that the description of the main types of penicillin product given in the paper will make it possible to choose the most appropriate product for any particular case.

"A point not mentioned in the paper is the claimant need for the adoption of a uniform system of expressing doses. Thus we find doses expressed as grains per pound, grains per kilogramme, grains per 20 lb. and grains per 100 lb. or milligrammes per pound, milligrammes per kilogramme, milligrammes per 100 kilogrammes and so on. Uniformity would simplify the calculation of the appropriate dose for any given animal and would also facilitate comparisons as to potency—and cost—between different compounds.

"With these introductory remarks I leave the paper to your tender mercies."

The Opener

Mr. A. H. Dawson, in opening the discussion, said that it was his privilege and pleasant duty to thank Professor Boddie for preparing and presenting the paper and to congratulate him on its excellence. The paper was a clear and timely warning to all concerned in the use or production of modern therapeutics. A discussion of the problems, so ably crystallised by Professor Boddie, might well make the paper an outstanding contribution to the Congress, and it was an honour to be asked to take part in it.

The author's assertion that no one had any right to use a drug in the treatment of animal disease who had not at least the information specified in his therapeutic postulates or yardstick—namely, evidence of pharmacological basis and details of therapeutic tests and toxicity trials—was a startling reminder of their responsibilities as professional men. It was, in Mr. Dawson's opinion, the most important statement in the paper and, if it were accepted, it was apparent from the angle of the clinician and patients that the requirements specified were certainly not too stringent; they were really bare necessities for the continued prestige of the profession and for the well being of the animals in their care. Considering the same statement from the manufacturers' angle, he could not think that any firm of repute would not be prepared to provide the evidence asked for regarding a new product.

Facilities for extensive field trials for new products, such as those mentioned by the author, were an urgent need, pending which they must continue to choose drugs as best they could and probably most of them would do so with a little more care and discrimination as a result of the paper than they had done previously.

The problem which confronted Mr. Dawson, and no doubt others engaged in practice, was, first of all, that of sorting out from the multitude of products offered those which to buy, and then of deciding which to use in any particular case. In an effort to decide which preparations to buy, reference to the trade circulars could be as confusing as it was time absorbing for in many of them one found a multiplicity of names for the same (or nearly the same) drug, all with claims to superiority portrayed by varying degrees of artistic achievement.

Though knowing nothing of the ways of big business, he believed that advertisements intended for the guidance of a learned profession would serve the purpose better if the strictly scientific approach were substituted for the spectacular. Why must drugs be marketed under trade names? If it were simply because the pharmacological name was too cumbersome for general use, would it not suffice to use a name approved by the B.P. or B.V.C.?

To call a drug by a name which could not become a household word would surely be an advantage over the present position in which the public were familiar with many of the remedies in use and, being familiar with them, lost faith and clamoured for something new and stronger. The element of mystery in the bottle of medicine dispensed by the veterinary surgeon, which had been so helpful in promoting confidence, now existed only in the mind of the prescriber.

The decision to try a new preparation was usually arrived at on the basis of reports of clinical trials. Clinical reports published by the commercial houses were, quite naturally, reports of apparent successes, and many of them were very helpful. They would be even more helpful if they told of some of the failures. A careful examination of some of the reports had left him with the impression that a successful conclusion of the cases might have been expected without resort to a preparation as expensive as the one used. It was, therefore, very difficult to assess the value of a particular agent on the information contained in the reports. Consequently, it was sometimes on a recommendation of the veterinary investigation officers of the Ministry, and sometimes on a clinical communication of one of the more adventurous spirits, as the author said, that they were encouraged to use it.

They might use a product because it was cheap and reputed to be equal to something which was known. Mr. Dawson thought it would not be inappropriate to relate an experience of his in that connexion. Some years previously he had used, purely as a long-term prophylactic, in two newly formed dairy herds, a quantity of S.19 *Br. abortus* vaccine. His suspicions as to its quality or the care with which it was marketed were aroused because there was no expiry date on the bottles. They were later confirmed by abortions occurring in the herds due to *Br. abortus* infection. Subsequent blood testing of a representative group of animals in each herd left no doubt that the vaccine failed to promote the formation of antibodies. He blamed himself for not having been more discerning, but could not help feeling that it should be made quite impossible for such a product to be marketed.

Another circumstance which could cause them to use a new product was that brought about when the manufacturer created a public demand for it by advertising it in the agricultural Press. They had recently seen a notable example of that which had been spoken about a good deal at Congress. Many of them would remember other examples.

Reaching a decision as to which drug should be used in a particular case was no new problem, but, as recent therapeutic advances had enabled them to apply specific therapy—as opposed to symptomatic treatment—to many different diseases and conditions the problem had become much more complex and much more important.

In dealing with the many conditions in the various species of animal they were called upon to treat they had to decide, usually in a mattter of a few minutes, not only which agent was the most likely to help in bringing about recovery, but also which agent was likely to do so in the most economical way. He made no apologies for emphasising the importance of economy in present-day veterinary medicine because it was certain that the future prosperity of agriculture depended largely on lower production costs of all its products, and they were bound to be involved in that.

It was unfortunate for them that the farmer could not calculate in monetary terms the benefits obtained from veterinary services. It might be the cost alone which the farmer considered and he would be looking for any marked increases. As far as such questions as pest control were concerned, rough calculations in relation to cost could be made; but no comparable calculations could be produced regarding the benefits of applying veterinary services, and it seemed likely that the farmer was going to look ever more closely at the costs he had to meet so that he might reduce his own cost of production.

It was not being suggested that expensive drugs should not be used, but that they should be used only after a careful consideration of the individual case and not simply because they happened to provide the specific and fashionable "cure easy" of administration. Again, when a specific remedy for a diseased condition was not known, or a diagnosis could not be made, the temptation to use the expensive remedies might well be more often resisted and resort to the old-fashioned method of symptomatic treatment employed, with emphasis on good nursing.

For economical use of the chemotherapeutic substances clinical skill must be backed up by laboratory examinations, and a near-at-hand laboratory service, able to undertake bacteriological examinations and sensitivity tests, was necessary. Mr. Dawson found that the services of a laboratory 80 miles away, efficient and highly valued as they were, were of little use in telling him what to do in a particular problem; rather, on account of the inevitable delay, they told him what he should have done which, unfortunately, was not always in line with what he had done and a certain amount of avoidable wastage occurred. Laboratory examinations and tests followed by specific therapy were not, however, the answer to all their problems.

In an outbreak of bovine mastitis which he recalled, the associated organism was a group C streptococcus which in repeated tests was found *in vitro* to be sensitive to penicillin but from which there was no response to penicillin therapy In fact, fresh cases occurred during the period when penicillin was being used prophylactically on clinically normal udders. He still did not know the reason for the failure of penicillin to deal with that infection of the udder by organisms shown to be sensitive to it, unless it was that it did not entirely reach the organisms or infection.

That would be a reasonable theory in the established cases of mastitis, in which the induration was so very marked, but could it be so for the clinically normal udder? They heard frequently from manufacturers of new bases for suspending intramammary antibiotics, which were reported as being great improvements, ensuring rapid and complete distribution throughout the udder tissue. Each intramammary product was claimed to be specially effective not because of the antibiotic content, regarding which each product was comparable, but by reason of a vaguely superior suspending agent or a longer exudation per tube or a greater volume per tube, of the inclusion of an enzyme or even the substitution of a capsule for the conventional tube. How did they decide which was the best of those variations? Professor Boddie might be able to tell them.

Regarding dosage of antibiotics and duration of treatment with them, Williams Smith urged the importance of using the minimal effective dose for the minimal time in guarding against the emergence of drug resistant strains of bacteria (THE VETERINARY RECORD. **69.** 751). It was realised that no hard and fast rules could be laid down to meet that requirement, but reference to dosage tables showed great variation in the doses given by different authorities, and is seemed that most practitioners in the uncertainty which existed tended to err on the side of the big dose. It should be possible to determine minimal requirements in the treatment of certain diseases which ran fairly true to type.

If Professor Boddie in presenting the paper had caused them to stop and think and be more critical in their judgment of present-day remedies, and if he had at the same time caused the manufacturers to realise that veterinarians were demanding more exact scientific information about the actions of their new products, he would have done a great deal towards resolving some of the problems of veterinary medicine. (Applause.)

The General Discussion

Mr. J. B. White (Salisbury) said he would like to record an observation made recently during the treatment of an outbreak of infectious ophthalmia in a group of about 50 calves. These calves were dressed twice a day with chloramphenicol eye ointment for a period of between a fortnight and 3 weeks. Most of the animals recovered without complication, but 4 or 5 had developed large deep ulcers of a type he had not seen before, and he wondered if this might be in some way be due to overdressing with chloramphenicol. He withdrew the treatment and substituted a cortisone product instead.

Recovery from this stage was very rapid, but whether this was due to withdrawal of the chloramphenicol or to the use of cortisone he was unable to say.

Mr. G. N. Henderson (Wimbledon) said: "Firstly, I must express my admiration for Professor Boddie's excellent survey of certain aspects of the therapeutic field, particularly his recommendations concerning the minimal data which should be supplied before new products are introduced. I must say at the outset that I fully endorse these particular remarks, but feel sure that the increasing interest being shown in the veterinary pharmaceutical field by British and American companies, will by the nature of the competition produced necessitate a more specific approach to the establishment of clinical effectiveness before products are made available to the veterinary profession. It is well known that the veterinary profession has a long memory where therapeutic products have failed to live up to their claims and this is naturally of great importance in considering the good will of the profession since failures are more often remembered than successes when deciding with which company to do business.

"I must contribute something to two particular points raised by Professor Boddie. Firstly, on the subject of phenoxymethyl penicillin with which I have had some experience in clinical trials. It is true that its use in the human requires administration every 4 hours if a satisfactory therapeutic blood level is to be achieved. However, in the two papers published to date covering blood level studies in animals, there has been recommended, in dogs at any rate, a dose of one tablet of 60 mg. of the free acid for a dog weighing 20 lb. and administered every 8 hours. The actual recommendations in the paper published by Jaksch, *et al.*, of the Department of Medicine, Veterinary College of Vienna in the *Wiener tierarztliche Monatsschrift*, 1954, volume 41, page 687, are given as 8 mg. per kg. bodyweight thrice daily, with a daily dose of 3 tablets of 60 mg. for a dog of 10 kg. bodyweight. A further paper published by Huenber, *et al.*, in the University of Pennsylvania Bulletin of October, 1956, confirms these finding and also discusses the use of phenoxymethyl penicillin administered either as single oral doses or as a drinking water additive for poultry. In these studies levels of addition were 6 mg. as a single oral dose for the chickens weighing between 3 and 4 lb. and wider medication on a free access basis of levels of 600 mg. per gal. In turkeys weighing between 10 and 11 lb. single oral doses of 30 mg. were given and the level of addition to the drinking water was again 600 mg. per gal. The findings of these workers indicated that at these levels of administration blood serum levels following single oral administration to fowls and turkeys were 2 to 6 times greater and with twice the

duration of those resulting from similar doses of potassium or procaine penicillin G. In the free access studies the medication of the drinking water produced blood serum levels 2 to 5 times greater with greater constancy throughout the group than those resulting from salts of penicillin G. In the dog, blood serum levels 3 to 8 times greater and less variable than those from the same dose of penicillin G salts were recorded. Further, in a paper published in the November issue of last year in the *British Veterinary Journal*, there were recorded some clinical findings using phenoxymethyl penicillin free acid in a series involving 84 dogs and 38 cats. Results indicated that oral administration of this drug produced clinical results parallel with those normally expected from parenteral therapy with the standard injectable penicillin products. Since this report, some work has been carried out administering one tablet of 60 mg. to suckling pigs daily for the control of certain scours and pneumonia. Present results are promising. Administration to young calves is also in an early stage and results indicate that in the young bucket fed calf where rumen development has not begun, oral administration of phenoxymethyl penicillin is of value in certain conditions.

"The second point where I must express some difference of opinion with Professor Boddie concerns the development of antibiotic resistance. While I accept that the administration of antibiotics in the form of feed supplements can, in some cases, produce drug fast strains of organisms, this resistance is surely confined to the antibiotic administered or its group (tetracyclines) since it is not likely or logical to expect that an organism which has acquired a resistance to the tetracyclines should show cross-resistance either to penicillin or streptomycin. I have no desire to side-track discussions of this excellent paper into the ding-dong conflict between those in favour of antibiotic supplementation of animal rations and those against it. What I would say, however, is that the present trend in antibiotic therapy surely shows a more realistic appreciation of their use and limitations. I certainly agree with the author in his recommendations that the more expensive antibiotics should not be used indiscriminately, particularly where the therapeutic range of penicillin or streptomycin or combinations of the two are equally effective and, of course, more economical. To my mind, however, the use of antibiotics should not necessarily be considered the prerogative of the clinician since these are, after all, merely drugs to be used for the benefit of mankind. It may be that the effect of certain antibiotics in promoting the growth of meat animals is of more significance in this respect than their use for the treatment of certain diseases; and if this is so, then the fact that such use produces drug fast strains implying that the antibiotic is no longer of value in therapy, should not surely automatically rule out this method of employing the antibiotic."

Mr. T. C. Denholm (Nottingham) said: "I would like to congratulate Professor Boddie on his very excellent paper. He has made several points which were long overdue and while some of our friends—at least I hope they are still our friends—in the commercial field may not agree with some of his remarks I think the subject was timely and necessary. He has stated that the main problem confronting the practising veterinary surgeon is to assess the worth of the new preparations. I would suggest that the next greatest problem is how to dispose of the flood of advertising material which arrives each morning by post. Some of this literature is quite useless in that it does not give us the information we need and seems to be issued on the basis of introducing a new washing-up powder to the housewife. Surely the drug firms realise that they are dealing with professional people who are entitled to a reasonable guarantee that the new preparation will in fact do what is claimed of it? I would like to endorse Mr. Steward's remarks. Surely it is only fair that firms should notify us of their startling discoveries before publishing them in the lay Press, or worse still, making them available to our clients?

"With regard to streptomycin Professor Boddie did not mention one unfortunate complication of its use. I refer to its tendency to cause emesis in many dogs and nearly all cats. This may be unfortunate in a patient already weakened by prolonged vomiting.

"Professor Boddie mentions the cost of chloramphenicol and then goes on to advocate its use in foot rot. I would suggest that it is equally expensive in this condition and some of us are not convinced that it is any better than 10 per cent. formalin.

"I was interested in the account one speaker gave us of the Alsatian bitch. We have a saying in Scotland that 'cobblers are the worst shod,' and it is sometimes said that the veterinary surgeon's dog is the most neglected. It is unfortunately true that the medical man's animal is often the most over-treated. While agreeing with Professor Banks that human and veterinary medicine should go forward hand in hand as one, I would suggest to our medical friends that when their animals are ill we are the people with the knowledge and skill to treat them. Too often they treat the patient themselves and only when the condition is advanced do they appreciate with some surprise that their efforts are not meeting with success."

Miss J. O. Joshua (Finchley) said that she would like to join in congratulating Professor Boddie on his excellent, and, in some ways, provocative paper.

She would like to endorse his remarks on the tendency to fly to antibiotics when often time other drugs would be equally effective, *e.g.*, the sulphonamides. She felt that often a sulphonamide could be prescribed initially when, failing response within 48 hours, recourse could still be made to an antibiotic.

As Professor Boddie had said, we were lucky in the relative absence of sensitivity reaction in animals to antibiotics; her faith had, however, recently been shaken by the occurrence of a violent urticarial reaction in a cat in response to two injections of penicillin (the cat had not previously been treated with penicillin). The acuteness of the urticaria was equalled only by its obstinancy in responding to treatment.

She would like to cross swords with Professor Boddie on his condemnation of the use of drugs with possible toxic effects and which might be only palliative. She was sorry he had singled out her old friend phenyl-butazone for attack in this respect. The longer she was in practice—and the longer she was a dog owner—the more she was impressed with the need for a modified approach to geriatrics in the small-animal field; she had come to realise that many old animals adapted well and led really happy lives despite decrease in physical activity, and it was in such cases, where a senile progressive disease such as arthritis was present, that she felt the use of palliative treatment was entirely justified.

Reverting to phenyl-butazone, she had been pleased to find, on first investigating the possibilities of the drug, that toxicity trials had been carried out in dogs; this was most useful to the veterinary surgeon. To the best of her recollection toxicity trials had been carried out in an adequate number of dogs, and over a long period. She believed that dogs were less subject to blood dyscrasias than man, hence the relative absence of toxicity of products such as gold and phenyl-butazone in the dog. Admittedly, phenyl-butazone could produce toxic side-effects—she had met occasional vomiting and one case of oedema—but this occurred quickly and the drug could be promptly withdrawn. Further phenyl-butazone acted rapidly and if a dog failed to show favourable response within 7 days then again the drug should be withdrawn. Dogs which tolerated the drug apparently did so indefinitely; it might be recalled that some 18 months ago she had recorded in the correspondence columns of THE RECORD the cases of two dogs which had received the drug for one year; one case was now off treatment for reasons not relevant but the other had now been on a dose of 600 mg. daily for 2½ years. As this was her own dog she hoped it might partly answer Mr. Denholm's remark about the cobbler's child! This dog, now well into her 12th year, was able to lead a happy life but she regressed immediately if the drug was withdrawn or dosage reduced.

She felt that if the drug was used with discretion it would be found most valuable in responsive and tolerant patients. Surely palliative treatment was justified, especially in ageing household pets?

Mr. R. Jones Pugh (Hounslow) said: "I must congratulate Professor Boddie on a most interesting and instructive paper.

XUM

There are, however, one or two points which I would like to comment upon.

"Firstly, Professor Boddie states that chloramphenicol can cause blood dyscrasias including agranulocytosis and aplastic anaemia. This is unfortunately true, but I think that he should have stated that such phenomena result from prolonged administration and/or over-dosage with chloramphenicol, and as far as can be ascertained from the lack of published reports in the veterinary sphere, such phenomena appear to have been proved only in man. Certainly, the application of chloramphenicol to pneumonic conditions in the human bears comparison with any other antibiotic with regard to the benefits obtained, but again it must be emphasised that over, or prolonged, dosage must be avoided. Concerning the administration of chloramphenicol to various conditions in animals, it is interesting to note that it was precisely this lack of evidence regarding the appearance of untoward effects in experimental animals, following high dosage levels of chloramphenicol, that a period of approximately 5 years elapsed before the presence of blood disorders was recognised *per se* to be a corollary to chloramphenicol therapy. In this respect, therefore, I would appreciate it if Professor Boddie would enlighten us as to whether or not any published evidence exists regarding similar results in any species of animals."

The Reply

Professor Boddie, in replying to the discussion, said that he was very pleased with the way in which the paper had been received. Many speakers had said kind things about it, and even those who disagreed with it in part did so in somewhat kindly terms.

The opener, in a reference to advertising, used the rather striking words that the strictly scientific approach should be substituted for the spectacular. That was a neatly expressed idea which covered much that was contained in the paper. More than one speaker had referred to the question of information on new products appearing in the agricultural and general Press before it was made known to the profession. He had read of one product in the agricultural columns of *The Scotsman* and it was not until three days later that circulars arrived through the post intimating the existence of this new product.

The extravagant use of a large number of expensive drugs was perturbing, and if they had criticised the manufacturers that day they should also turn some criticism towards themselves in relation to economy.

The opener raised an interesting point on response to antibiotics in mastitis. Probably all of them were familiar with the work which Blackburn was doing on the pathology of mastitis. It confirmed that there was difficulty in ensuring that a small quantity of penicillin when put into the teat of a cow found its way into a remote corner of the udder. The opener had pointed to the futility of some products but had not mentioned the colour of the label on the bottle, which was, of course, important!

Professor Boddie could not agree with the statement that the B.V.C. over-stressed purity. The standards of purity it demanded were not too high at all

The use of chloramphenicol was a subject, touched on only briefly in the paper, which had provoked quite a lot of controversy. It was like the splinters one got caught in the finger in that the small ones which could not be seen caused the trouble. Having listened to the discussion, he rather wished that chloramphenicol was not referred to in the paper. It was not really important. Some speakers seemed to have missed the point. Chloramphenicol, when used on a large scale, could be prohibitively expensive, but if it were used locally in the form of a 10 per cent. solution it was not expensive if it produced the desired results. It was not usually necessary for a long course of chloramphenicol to be given. Toxicity tests with chloramphenicol in small laboratory animals do not necessarily give an indication of its possible toxicity in domesticated animals.

While Mr. Henderson had given them very interesting information on penicillin V, phenoxymethyl penicillin, it did not appear to affect materially any statements made in the paper. The paper was not intended to indicate that there was a cross-resistance of antibiotics developing between groups; there was cross-resistance within certain groups.

Miss Joshua's experience in dealing with a cat suffering from urticaria was interesting and it would be useful to know whether the cat had ever been treated with penicillin previously. One might derive some sort of negative satisfaction if it had been. Miss Joshua had rather joined issue with him on drug toxicity and produced what might be called a very convincing argument in favour of trying to smooth the path of ageing dogs when it was known that the remedy used was toxic. Whether her argument should be applied to younger dogs might be a different matter. The case put by Miss Joshua was rather undermined by her admitting that the drugs concerned were toxic and there was a need for caution. That was surely in keeping with what was said in the paper.

Mr. Cook had introduced a lovely, cool draught of commonsense, and Professor Boddie could only say he was very much in agreement with it, particularly with the point that animals had sometimes recovered from disease before the days of sulphonamides and antibiotics. It was apt to be forgotten that an antibiotic acted against the cause of the disease, that the animal was ill before it was treated, and it was ill because of the tissue changes produced by the organisms. When the organisms had been got rid of the tissue damage was still present and required time to repair, and the patient had still got to be nursed. To take an extreme example of pyelo-nephritis in a cow, the cause of the disease might be removed, but the tissue changes which had taken place might be irreparable. Mistakes could often be made when an animal's temperature dropped after the use of antibiotics and it was regarded as quite well. The curative process took time.

The importance of diagnosis was quite rightly stressed by Miss Uvarov. As to her reference to a 50 per cent. response to a drug, should that really be regarded as a response to the drug at all? (Applause.)

The Chairman thanked Professor Boddie and Mr. Dawson, and the meeting concluded.

The Role of Immunology in Biology and Medicine

BY

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AT the beginning of this century, immunology, then an infant barely 10 years old, promised to be the wonder child of medicine. There were few branches of medicine that would not feel the impact of this vigorous development, the study of which might even disclose the formula of a panacea. This hope, naturally enough, was not realised; nevertheless, there were fields in which immunology captured and maintained a leading position. The potentialities and scope of vaccine prophylaxis were, and of course still are, major weapons of medicine. Although serum therapy did not fulfil its earlier expectation, where toxin neutralisation was required, it was, and still is, an important and integral part of therapeutics. Again, serodiagnosis has not fallen short of its early promise. Then why, by the time of the Second World War, had a certain lethargy fallen on the subject?

In my opinion, three reasons contributed to this:—

1. *The advent of antibiotics and chemotherapeutic agents.*

   This brought the mistaken view that the immune responses of the host could be completely by-passed and needed no further study; also, perhaps, that the exact diagnosis and recognition of the type of causative organism was not so important.

2. *The lack of fresh biological concepts.*

   I feel that the important contributions on the physical and chemical aspects of the antigen-antibody interaction in the previous decade had captured too vividly the imaginations of young workers with the result that the biological issues were neglected.

3. *The way the subject has been taught.*

   In the main, immunology has been taught to medical and veterinary students only and, in the few lectures allocated to it in the bacteriology course, only the applied aspects could be covered. Also, many of those responsible for the teaching were primarily bacteriologists and only superficially acquainted with the subject themselves.

I think, perhaps, these doldrums were good for us, for they acted as a stimulus and challenge. Now the tide of interest is coming in again and the subject is once more attracting young workers. However, immunology has still to find its proper place in the teaching curriculum. Its scope is so much broader than the narrow significance conveyed by its continued colonial status in the imperial departments of bacteriology. I shall try to show in this lecture that immunology ought to have received dominion status long since and should now be considered and taught as a science in its own right—as is physiology.

Immunology as a Science

In claiming the status of a separate science for immunology, we should, perhaps, first define what we understand by a science. Woodger (1948) defines it as a "systematised body of propositions about some subject matter or other enshrined in books or in the minds of individual men." The subject matter of a science is arbitrarily defined and must have no hard and fast boundaries. However, frontiers, even though ill-defined, are necessary for our convenience, otherwise all of us would still be natural philosophers.

No science, at its inception (unless it is to prove sterile), can be expected to have its subject matter clearly delineated, yet the science is christened for all times at this early stage, so in discussing the subject matter of immunology, it should not be surprising that this extends far beyond studies on immunity. To give some idea of the compass of the subject, I think one could say that immunology accepts responsibility for all studies connected directly or indirectly with natural and acquired resistance and further—and this is important—for any biological phenomenon involving reactions of a fundamentally similar nature. Also, immunology would claim, as in its province, any problems, biological or chemical, which could be investigated by methods or techniques used in serology. The main reagents of serology, as you know, are antigens and antibodies and also other serum factors involved secondarily in antigen antibody reactions.

I thought that the best way of emphasising the rôle of immunology in both biology and medicine would be to discuss, very briefly, various facets of the subject which I feel illustrate this thesis. In doing this, I shall try to emphasise the constant swing, as of a pendulum, backwards and forwards between academic studies and practical applications, between the strictly biological interest and the strictly medical interest, and between human medicine and veterinary medicine.

Serology in the Recognition of Antigens

I shall begin this brief survey with serology, and here, I think, the greatest application to-day, especially in the biological field, comes in *the use of characterised antisera for the recognition of antigens.* The vast amount of work on the serological classification and identification of bacteria and viruses, of course, comes under this heading, and the briefness of my remarks in this connexion is certainly inversely proportional to its obvious importance. The serological classification of the animal kingdom by precipitin tests as originally studied by Nuttall (1904) here in Cambridge in 1902, emerges from its purely academic interest, when applied to the problems of deciding, for instance, the public health question, whether beef sausages have been contaminated with horse meat or, on what species of wild animal a tsetse fly last fed before being captured in the jungle (Weitz, 1956), or, in forensic medicine, whether a blood stain on clothing is of human or animal origin.

Not only can different species of the animal and plant kingdom be identified and classified by serology, but it is also a tool for distinguishing between individual members of the same species. Landsteiner, in 1900, divided man into groups by virtue of a characteristic of the red blood cells and a substance in the blood plasma antagonistic to the red cells of a different group. These characteristics of the red blood cells, which we now call blood group antigens, are genetically determined molecular compounds which, by virtue of their antigenicity, are readily identified by serological tests. The importance of the blood group antigens to medicine was first recognised when it was shown that blood used for transfusion had to be compatible if transfusion reactions were to be avoided. No longer are there just the 3 blood group antigens in man, but at least 50, and this number increases almost monthly! The fact that these antigens are inherited, according to Mendelian laws, brings a mass of new material to the field of human genetics.

A further clinical significance of the blood group antigens came to light in 1941, when it was shown that haemolytic disease of newborn infants stemmed from blood group incompatibility between mother and foetus; the mother producing antibodies against the red cells of the foetus. With proper ante- and postnatal serological tests, these cases can now be anticipated and, if indicated, exchange transfusion carried out promptly at birth. Where the blood group antigens are also on tissue cells, other consequences of incompatibility between mother and foetus could be expected. Incompatibility on the Tja antigen system has been reported to be associated with repeated miscarriage, and whether the blame for some forms of infertility can be ascribed to ABO incompatibility, is still *sub judice*. The aetiology of Mongolism has even received consideration in this connexion (Penrose, 1946).

Animal Blood Groups

Veterinary medicine was not to be outdone as far as haemolytic disease of the newborn was concerned. First, in France, the haemolytic anaemia and jaundice of newborn mule foals was snatched from the preserves of the protozoologists and was shown to be due not to piroplasmosis, but to an immunisation of pregnancy following, in this case, inter-species blood group incompatibility. Then reports from Newmarket and America showed the condition in Thoroughbred horses. Again, in the pig, the syndrome was first recognised in the field in this country by members of the Veterinary Investigation Service, and the disease in this species has since been thoroughly investigated at the Veterinary School in Cambridge. The condition has been produced experimentally in dogs by a medical team in America but, to my knowledge, there has been no authentic report of the disease occurring naturally in dogs.

The occurrence of haemolytic disease of the newborn in animals has greatly contributed to the recent work going on in many parts of the world on animal blood groups. This country is struggling to maintain a position in this field, and it is gratifying to know that cattle blood groups are being studied by an active group in Edinburgh, horse blood groups at Newmarket, pig blood groups at the Veterinary School in Cambridge, and sheep blood groups at Babraham.

Investigational work on animal blood groups goes on in the closest liaison with human blood group research, bringing together in the field of immunogenetics, the serologist, the geneticist, and the statistician. The compilation of knowledge on animal blood groups should be of great interest to those concerned with animal breeding. Not only can the blood groups be used for parentage testing, but the recognition of gene frequencies in the different breeds and the linkage of blood factors to other constitutional characteristics must, in time, pay useful dividends for one is, in effect, measuring, objectively, some of the physical characteristics which make up individuality.

I do not think that, even in the sanguine atmosphere of the beginning of this century, it could have been foreseen that there would be a common meeting ground between serology and physical anthropology. And yet the blood group antigens, being measurable physical characters and subject to simple genetic control, are important and objective data of the utmost value to the physical anthropologist (Mourant, 1954). The serological tool does not always unearth the expected. For example, although, according to tradition, Iceland was settled by Vikings from Norway, the distribution of the blood group antigens, in the present-day population of Iceland, resembles, more closely, that of the Irish than that of the Norwegians.

Smoking is not the only thing which appears to have an association with cancer. Recent work of Aird and Bentall (1953) indicates a correlation between cancer of the stomach and a blood group character. Other diseases are also being looked into for an association.

Surgery and Immunology

Surgery would seem to be remote enough from immunology, yet certain of its major problems bring it within the professional interest of the immunologist. Grafting of donor skin is undertaken as a life-saving procedure for severely burnt patients, but such homografts, that is, grafts between individuals of the same species, will not " take " permanently except where the donor and the recipient of the graft are identical twins, having an identical genetic constitution. In cases of severe burn, even the limited survival of the graft is valuable, but the advance would be momentous if one could get a skin homograft to " take " permanently. It is now generally accepted that the " throwing off " of a homograft is the consequence of an immunological reaction of the host against the genetically foreign tissue antigens of the graft. The demonstration and characterisation of these tissue compatibility antigens will probably require very specialised techniques and is certainly a great challenge (Billingham *et al.*, 1956).

Owen (1945), working on cattle blood groups, an apparently unrelated field, observed a very strange phenomenon in freemartins. He found that these non-identical twin cattle which had had fused chori-

onic foetal circulations, possessed two sets of blood elements in their circulation—the animal's own and that of its twin. The strange fact was that the host was not reacting against the genetically foreign blood cells of the twin, which we may regard as a homograft.

Burnet was quick to emphasise the significance of Owen's observation and harnessed it to support his theory of antibody formation. According to Burnet, the body produces antibodies only against substances which it recognises as " Not Self " or foreign, but the body's ability of recognising what is " Self " and what is " Not Self " develops, he conjectured, only at the end of the foetal period and so genetically foreign cells, gaining access to the body, while the body is still in the foetal stage, are automatically accepted as " Self " and are thus able to survive in the host, unmolested by any immune reaction of the host. In the case of the dizygotic cattle twins, primordial blood cells of one foetal twin cross over *via* the fused chorionic circulation to the other foetal twin. These cells settle down and become accepted as " Self " in the new host, with the result that the adult has two genetically distinct types of blood cells and is a blood chimera. A chimera, in scientific language, is an animal (or plant) built up of genotypically different tissues. The name is derived from the Chimera of Greek mythology—supposedly a fire-breathing female monster resembling a lion in the fore part, a goat in the middle, and a dragon behind.

Billingham, Brent and Medawar (1953, 1955) put this hypothesis of Burnet's to the test with skin homografts in experimental animals and showed that if live skin cells of a donor animal were injected into a recipient while it (the recipient) was still a foetus, subsequently, in post-natal life, the recipient would *tolerate* genetically foreign homografts from the same donor. Billingham, Brent and Medawar have called this phenomenon *actively acquired tolerance*, and as a concept of a specific inhibition of response it is, as you can appreciate, the complete antithesis of actively acquired immunity. This is, I think, by far the most important biological concept which has enriched immunology for a long time. Although it offers no obvious practical solution to the problem of transplantation of skin or other organs in man, it does show that the the ramparts are not impregnable. It is, perhaps, salutary to remember that in this atomic age the question of bone-marrow transplantation is not of academic interest only.

Gel Diffusion

Before leaving the part of this discussion on biologically interesting antigens, I should just mention the great technical advance which gel diffusion methods (Oudin, 1953) have brought to the detection, analysis, and characterisation of soluble antigens in complex mixtures. By allowing complex antigen mixtures and corresponding antisera to diffuse against each other through an agar medium, individual precipitating lines occur corresponding to the number of reacting systems. The method, and there are many modifications of it, is admirably suited for such problems as the testing of toxin or enzyme preparations for purity, for analysis of the complex antigenic structure of bacteria, or the analysis of the antigenic components in pollen extracts which may be concerned in hay fever. Such tests bring the immunologist to the service of the biochemist or physical chemist, for these immunological methods may detect impurities in protein solutions which, by physical methods alone, appear to be absolutely homogeneous and pure.

Antibody Detection

Up till this point, we have been considering the use of standardised antisera for the recognition of antigens. We must now look at the reverse side and consider the various aspects of *antibody detection using known antigens*. Under this heading we find ourselves confronted with the whole field of serodiagnosis, making use, as it does, of agglutination and complement fixation tests as well as specific inhibition tests of virus haemagglutination. As a result of comparative studies on different animal species (Blomfield *et al.*, 1949), we now know that much more sensitive results can be obtained in complement fixation tests if we select the complement to be used according to the species-origin of the antisera to be examined. It should not be surprising that cow antibodies, for instance, behave differently in this and other respects from cat or human antibodies. Also, a negative simple agglutination test can no longer be taken as sufficient evidence for excluding the presence of antibody for we can now unveil, by more specialised techniques (Coombs *et al.*, 1945), antibodies which do not agglutinate and which have merited for themselves the epithet " incomplete." The wheel is turning away from the " unitarian concept " of antibodies (Zinsser, 1931), and towards the view that there may be a whole spectrum of antibody types directed against the one antigen.

It is a fact, I think, that in human medicine to-day, diagnosis of infective diseases is not so dependent as previously on serological tests. This is largely because of the improved cultural methods used in bacteriology. In veterinary medicine, I imagine serodiagnosis plays a greater rôle. On the other hand, epidemiological work, especially in connexion with the virus diseases, seems to be more dependent than ever on antibody measurement. However, the pattern of serodiagnosis in human medicine is changing, and it is falling more and more within the field of immuno-haematology.

Immuno-haematology

Immuno-haematology, as its name implies, is a hybrid of immunology and haematology which has already proved its vigour in both clinical and experimental medicine. It has also succeeded in attracting powerful patrons which are always needed where research is concerned. Under such patronage blood dyscrasias with a suspected immunological basis are studied such as, for instance, acquired haemolytic anaemia, certain forms of thrombocytopenia and leucopenia, the blood manifestations of lupus erythematosus and rheumatoid arthritis, and experimental studies on leukaemia and even haemophilia.

Antigen-antibody Interaction

Sometimes it is neither the antigen nor the antibody which is under investigation, but rather the actual interaction itself. This is very much the concern of those who work on what the French call "*sérologie proprement dite*," and also of the immuno-chemist who studies the antigen antibody reactions from the chemical point of view. The significance of such studies lies not only in the esoteric interest of the immunologist but also in that antigen-antibody reactions may serve as prototypes for other biological reactions. One cannot but help being struck, for instance, by the points in common between antibodies and enzymes—their remarkable specificity, their protein natures, and their reactions with antigen or substrate. As bizarre examples of strictly biological phenomena which may fall into the category of antigen-antibody-like reactions, are fertilisation in lower animals (Tyler, 1948), and the mechanism of self-sterility in plants (Lewis, 1949). In the fertilisation process of sea-urchins there is a very specific interaction of the egg-water and spermatozoa which is, amongst other things, also able to produce agglutination, precipitation, and even complement fixation. In the second example, there is an equally specific reaction between protein material in the style of the plants and an antigen-like substance in the pollen grains.

Immunity

The antigen-antibody interaction brings us back to medicine again and to the problem where the science of immunology began, namely, immunity. Here, we must be prepared to leave the test-tube and go back to the animal. The study of immunity is a vast field for, although there are general principles, a separate study has to be made with each infective organism and, with each organism, for each species of animal.

Immunity to helminth and protozoal infestation is a separate and most interesting chapter of both biology and medicine with the constant struggle between adaptation on the part of the parasite and the defence mechanism of the host. Veterinary parasitologists are, at the present, making most valuable contributions to this field.

Factors, other than antibody, are also concerned in the build-up of immunity, and the ways of stimulating so-called non-specific immunity are very much in the public eye at the moment. Properdin (Pillemer, 1955), immuno-conglutinin (Marks & Coombs, 1957), and other non-specific factors are being actively investigated as to the part they play.

Antibody synthesis is of interest not only for those working on immunity *per se* but also for the biologist concerned with adaptation, for antibody synthesis is a singular example of a strictly adaptive process transferable from one cell generation to another. Again, antibodies being globulins, may serve as a good model for studies on protein synthesis.

Auto-antibodies in Disease

While on the subject of antibody formation, I will remind you of the biological law which echoes the observation that, under normal conditions, the body does not produce antibodies against its own component antigens. That the body does not intoxicate itself by such a process was first enunciated by Ehrlich in his famous concept of *Horror Autotoxicus*, and Burnet's concept of "Self" and "Not Self," is another way of expressing the same law. However, it rather looks, from recent work, that we are going to witness some abnormalities or dysfunction of the antibody producing system, for examples of what appear to be auto-antibodies, that is antibodies directed against the individual's own component structures, are presenting themselves in both clinical and experimental medicine. We now have what appear to be auto-antibodies to red cells in acquired haemolytic anaemia, auto-antibodies to thyroglobulin in chronic thyroiditis (Witebsky *et al.*, 1957), a reported example of auto-antibodies to adrenal tissue in Addison's disease (Anderson *et al.*, 1957), auto-antibodies to cardiac muscle associated with cardiac infarcts (Dombusch, 1957), and auto-antibodies to spermatozoa (Freund, 1953). It is not yet certain whether the auto-antibodies are associated with the cause of the disease or whether they are simply the consequence of an existing pathological lesion.

Even on this question of auto-antibodies, which appear to be abnormal and to belong to the realm of pathology, we are brought back to the strictly biological field by the work and ideas of Tyler (1946) and Weiss (1955), who consider, that as part of the careful regulatory mechanism of the body, auto-antibodies, or substances comparable to them, are concerned in the formation of cell structure, growth, and differentiation.

Immuno-therapy

Both time and inexperience prevent me from expanding on the more practical side of the use of vaccines and other forms of immunotherapy in the prevention and treatment of diseases. This is a field, anyway, which is too obvious to require emphasis. I would only stress that there can be few methods of treatment which have such a physiological basis.

Allergic Phenomena

A most important section of immunology of great concern to medicine is that dealing with allergic phenomena, where antibodies having very special properties become associated with tissue cells and which, in the presence of antigen, set off a chain of reactions, in many cases markedly detrimental to the host. In most infective diseases, the allergic responses of the host help mould the pathology of the disease, and may, of course, incidentally, be taken advantage of in the form of diagnostic skin tests.

Then there are what we might call the strictly allergic diseases where the offending allergen or antigen *per se* is usually an innocuous substance such as pollen, skin dander, or simple drugs. In the atopic group of allergies such as hay fever and asthma, where most of the clinical symptoms are referable to the histamine and histamine-like substances liberated by the antigen-antibody reaction, there is a need for

the closest collaboration between the clinical allergist, the pharmacologist and the immunologist and also, on account of the undeniable rôle of psychosomatic factors—the psychologist. Most of the allergic diseases of the skin belong to the so-called delayed type of allergy and here, of course, the immunologist must seek the dermatologist as a colleague.

It is not uncommon to hear those who teach immunology being rather scornful of clinical allergists, but really it is the academic immunologists who should be humbled at their own failure to get the fundamental issues and understanding of allergy in man and animals on a more scientific basis. The fact that there is no way, as yet, of measuring, *in vitro*, the antibodies causing the sensitisation in hay fever or asthma, the antibodies presumed to be involved in drug reactions or the antibodies causing allergic contact dermatitis, is evidence enough of our ignorance.

Besides the primarily allergic diseases to which I have just referred, there is a steadily enlarging group of diseases which, depending on definitions, probably have an allergic or immunological basis: the rheumatic group of diseases, glomerulo-nephritis, multiple sclerosis, sympathetic ophthalmia, lupus erythematosus, and other members of the so-called " collagen group of diseases."

Immunology and Cancer

Now, finally, we must pass on to cancer. Ever since the earliest days of immunology, the early diagnosis of cancer by serological methods and treatment by immunotherapy have haunted the thoughts and aspirations of countless investigators. Many have claimed success and forfeited their reputations! As a younger worker myself, I was strongly warned to steer clear of this Lorelei of the young immunologist. But to-day, no less an authority than Burnet (1957), is putting forward an immunological theory of cancer in line with that of Green (1954), and distinguished immunologists, such as Witebsky *et al.* (1956), are taking up again their earlier studies on the antigens in normal and malignant tissues. Here, the pendulum continues to exert its controlling influence and swings back to the biological field again, for the theories of Burnet and Green centre around the loss of " self-marker " tissue antigens and an upset in the balance of auto-antibody-like substances which normally control growth.

In Conclusion

Here I must conclude this discussion. I have tried to convey the scope of the subject and its relevance to other sciences without going into the intricate technical details which are, of course, such a joy to the specialist only. I hope I have been able to show that immunology is as much an integral part of biology as of medicine.

It was Claude Bernard who stressed so strongly that if medicine were to be both scientific and experimental, it must make use of the comparative approach. In immunology, the comparative approach is used almost unconsciously, and although this, in the past, has led to a certain amount of confusion, I feel it has also assured the foundations of immunology as a truly experimental science.

The full appreciation of the scope and significance of immunology raises the consideration of how it should best be taught, as I have already mentioned. One does not train a biochemist by merely doing a few urine or blood analyses, nor can we expect to inspire young graduates with immunology by three or four lectures on certain applied aspects of the subject of immediate interest to bacteriology only.

May I end by quoting that great master, Ehrlich. In 1906 he wrote: " I am convinced that the influence exerted by my theory "—he is talking of his theory of antibody production—" will extend far beyond the limits of pure immunity studies and that it is of considerable significance for an appreciation of vital phenomena . . . It has been shown that the substances obtained by immunisation are nothing but the tools of normal cell life, tools which we can thus isolate from their place of production and subject to an individual examination."

The Chairman of the session was Sir Alan Drury, F.R.S., to whom the essayist paid tribute for early encouragement in his own studies, before reading his paper.

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Some Aetiological Factors in Diseases of the Young

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IT is a common observation that the susceptibility of man and of animals to some infectious diseases varies according to the age of the individual. This susceptibility may be at its height in the very early days of life and decline with increasing age. On the other hand an extreme susceptibility may become apparent during some phase of development of the individual or during old age. The biological and physiological state of the host is as important as the nature of an infecting agent and this implies a multiplicity of causes in infectious diseases. Thomson (1957), who has written of the changing pattern of disease, says of tuberculosis, " With the discovery by Koch in 1882 of the responsible organism, the general medical view was that the epidemiological picture of the infection was complete. But it is now appreciated that tuberculosis, like other diseases, is of multiple causation and the way to complete control is long and arduous."

Bacteriological thought has experienced a marked change and the fixed ideas as to what is a pathogenic bacterium are no longer held. More attention is paid to bacterial physiology than formerly and the mechanisms of pathogenicity attract more interest than the lesions finally produced in an animal. The selectivity demonstrated by bacteria and their products has also intrigued research workers. Toxins attack certain tissues and bacteria tend to be localised in selective tissues.

This specific activity of toxins is shown by the direct effect of botulinum toxin and tetanus toxin on the neuronal elements in the nervous system ; the former acts exclusively upon the cholinergic nerve endings in the peripheral somatic and autonomic fibres, the latter operates only upon nerve cells in the cerebrospinal axis itself (Payling Wright, 1955). Less exact knowledge has been acquired with some other infections associated with the invasive properties of bacteria ; an approach has been made by estimating the microbial population of different organs of an animal after the introduction of a measured dose of bacteria. As an example, we know that *Corynebacterium renale* is capable of multiplying in the kidneys of mice after an intravenous inoculation of a sufficient dose of living organisms. There may be some slight growth in the lungs and spleen during an initial phase but the selected tissue is the kidney medulla (Lovell & Cotchin, 1946).

The trend in bacteriological research to-day is towards an understanding of the physiology of bacteria. The metabolic activities and the nutritional requirements of bacteria are neither fixed nor stable. They depend for both on their enzyme content which is capable of adaptation ; constitutive enzymes are always produced by a given organism whatever the medium in which it is growing. On the other hand the adaptive enzymes are subject to some limitation ; they are associated with living cells and they appear in a given bacterium as a result of growth in a medium containing their specific substrate. Many of the toxins and toxic fractions of pathogens are adaptive enzymes and they appear in a host only when the bacterium is growing in specific tissues and under certain conditions. There is thus considerable and constant variation in the relationships between bacteria and their animal hosts. Bacteria can adapt themselves, and therefore our former fixed views of what is a bacterial pathogen must be modified. A definition of pathogenicity as stated by Miles (1955) is suitable for our purpose ; it is " an index of the behaviour of a microbe either within the tissues or on the surface of a given host in a certain agreed or defined state of health." This " state of health " of the host is therefore an important factor because it is in this specific state that the pathogen is able to interfere with, and derange, the structure and metabolic process of the host. Age is a factor in this " state of health " and a significant one in the aetiology of many infectious diseases. It may be associated with a developmental phase and the age itself be of secondary moment. Sexual development is of primary importance in Brucellosis, and the susceptibility of heifers and the apparent resistance of children, calves, lambs and kids to the disease fits this picture. General debility, faulty feeding and lack of a specific immunity may influence the diarrhoeas of infancy, whether they be of babies, lambs, calves or pigs, but these alone cannot satisfy those conditions which enable certain bacteria to grow in the tissues of the young and yet be held in check in the tissues of adults.

Age must therefore be considered in infantile gastro-enteritis, scours in calves, lambs and piglets, bacillary white diarrhoea of chicken and Johne's disease of cattle. Some of these disorders have as a specific cause a bacterium which is regarded as pathogenic ; in others the infective agent is regarded normally as non-pathogenic. *Salmonella pullorum* and *Mycobacterium johnei* are considered to be pathogenic and some would assert *Escherichia coli* to be non-pathogenic. Is there any justification for this differentiation ? It is difficult to initiate bacillary white diarrhoea in healthy day-old chicken under experimental conditions ; *Myco. johnei* may be recovered from healthy cattle ; many types of *E. coli* are clearly the causal bacteria in cases of intestinal disorders of babies, calves, pigs and probably lambs. These bacteria must therefore be considered in relation to the host in which they are found. Each is widespread in nature and each is concerned with a disease in which the physiological status of the host is an important though often neglected factor. These intestinal diseases are largely endemic and the causal bacteria are present in the neighbourhood and frequently in the adult population. Infection should be regarded as the normal state ; it is the disease which is abnormal.

Infantile Gastro-enteritis of Babies and White Scours in Calves

There are some similarities in these conditions ; in babies the disease may follow the collection together of

susceptible infants in a hospital or institution. Infants from the slum areas of a city and those which are bottle fed appear to be prone to the disease. Specific types of *E. coli* are recoverable from most of the outbreaks in wards and nurseries and the common age of the sick babies is from 2 to 8 months. Two of the specific types are known to have been associated with diarrhoea in aged individuals debilitated by disease. It is within the past 12 years that attention has been focused upon these specific serological types of *E. coli*. They are identified according to their " K " or surface antigens, their " O " somatic or body antigens and in some cases the " H " flagella antigen is considered. In 1947 it was recognised that a serological type belonging to O 111 was the most frequent one observed in this country. This type is of much less frequency to-day and other types belonging to " O " groups 55, 26, 119, 128 are or have assumed importance in the matter of frequency.

TABLE I

INCIDENCE OF 5 SEROTYPES IN ENGLAND AND WALES (1955–6)

	(BABIES) 0·26	0·55	0·111	0·119	0·128
1955					
Sporadic cases ...	438	444	321	248	211
Outbreaks ...	82	252	143	193	117
Total	594	905	692	585	411
1956					
Sporadic cases ...	501	396	279	340	114
Outbreaks ...	57	215	98	127	18
Total	641	824	496	608	148

Figures compiled from those reported to the Epidemiology Department P.H.L.S.

Some figures compiled by the Epidemiology Department of the Public Health Laboratory Service show the frequency of five serotypes in England and Wales for 1955–6. O 26 is responsible for a large number of sporadic cases and suggests that its distribution is extensive ; this type is relatively common in calves.

TABLE II

INCIDENCE OF SEROTYPES IN ABERDEEN AREA (1947–54)

	(BABIES) 0·111	0·55	0·26	0·119	Others
1947 ...	233	38	—	—	—
1948 ...	30	67	—	—	—
1949 ...	8	109	—	—	—
1950 ...	2	65	9	—	—
1951 ...	1	74	3	—	—
1952 ...	5	4	2	21	—
1953 ...	0	1	20	0	1
1954 ...	0	0	14	0	1

(see Smith, 1955)

The comparative frequency of four of the types in the Aberdeen area for the years 1947–54 is shown by the figures compiled by Smith (1955). O 111 has virtually disappeared ; O 55 assumed importance and reached a peak in 1949 and has since become less frequent and O 26 has increased in frequency during the later years.

The calf disease, white scours, was described by Jensen in 1893 and, according to him, it had already been recognised for 100 years. He appreciated the significance of *E. coli* in its causation ; this has been confirmed by Theobald Smith and his collaborators in U.S.A. and by groups of workers in this country. *E. coli* is capable of killing calves under certain conditions and the method employed and recorded by my colleagues at the National Institute for Research in Dairying and at the Royal Veterinary College, London, is successful. Calves are collected and placed in special pens ; none is accepted which has suckled. Some calves are given stored colostrum and others are deprived of it ; white scours develops spontaneously in those deprived of colostrum and may spread to those which received it. The disease occurs constantly in what one might describe as an enclosed community subjected to the frequent immigration of fresh susceptible calves. It bears some comparison with the outbreaks of infantile gastro-enteritis which " follows the collection together of susceptible infants in a hospital or institution." The calves which die are examined *post mortem* and the cultures of *E. coli* recovered from bone-marrow, blood and other sites are examined by serological means. Since 1950 a number of serotypes have been established and many have received international recognition. Within the " enclosed community " we find a constant change in the serotype which dominates the scene. One type which is recovered most frequently ceases to be the common type ; a type found in one season may disappear or reappear next year.

The experience obtained in these experiments is being applied to natural outbreaks and material and cultures are received and examined. Some of those types met with under experimental conditions are found in the field and there are, in addition, some newly established ones. To-day my colleague, Dr. T. A. Rees, searches for 26 different types and I am indebted to him and to my former colleague, Mr. P. C. Wood, for the figures given in Table III.

TABLE III

INCIDENCE OF 7 SEROTYPES IN CALVES 1950–6

	0·114	0·26	0·35	0·9	0·78	0·15	0·137	Others
1950/1	14	9	21	15	—	—	—	6
1951/2	0	26	16	80	23	11	—	38
1952/3	0	14	3	1	27	8	—	11
1953/4	0	0	1	0	5	0	—	1
1954/5	0	5	1	0	2	1	22	45
1955/6	0	2	3	1	13	3	2	18

The numbers given in the seasons 1950/1 to 1955/6 are the totals of 7 of the serotypes of *E. coli* isolated from calves. They are the collective ones from the calves in our " enclosed community " and from calves in the field which have died from white scours. Some of the common types tend to disappear and others increase in frequency and then become less common.

This is another similarity between the human and animal disease ; it may, of course, be argued that the figures given in both are not representative. There is, however, no doubt that the number of types of *E. coli* which have demonstrated their pathogenicity is increasing. Six or more types are recognised in the human disease and more than 20 in the calf condition. It suggests that a very large number may eventually demonstrate their potentialities as pathogenes. The

phenomenon of an increase is virulence by passage is well known but the possibility here is that this increase in virulence may be associated with an antigenic change or evolution.

It is nearly 30 years since Griffith recorded his observations with pneumococci in mice. A rough non-capsulated type 2 acquired the capsule of type 1 within the peritoneal cavity of the mouse. This change was produced by other workers in the test tube at a later date. It showed that a bacterial cell which had lost its power to synthesise a capsular substance could gain the power to synthesise a different one in a suitable substrate. To-day it is possible to induce other species of bacteria to acquire new serological characteristics ; they may also acquire new enzyme properties and vary in their degree of resistance to drugs. Bacterial mutation is accepted and bacterial genetics recognised as a serious study.

This leads us to consider the basis of pathogenicity. There is little exact information except in certain infections ; the Gram-negative bacteria are amongst the most puzzling. The dead cells and endotoxins of many of the Salmonella are no more toxic than those of *E. coli* ; toxic chemical extracts of *E. coli* show no difference whether they are prepared from virulent or avirulent strains. (Carne. personal communication.) It is apparently the ability to survive and to multiply in the animal's tissues which constitutes the important attribute of the virulence of a strain. This aspect of pathogenicity is often associated with a surface antigen such as the " K " antigen of *E. coli* ; the substrate or medium in which it grows is consequently worthy of study and investigation. Conclusions which are drawn from studies made in the test tube cannot replace those made in the environment in which the bacteria grow and produce disturbances. New techniques are required studying the conditions whereby bacteria will grow in these substrates.

The antigen-antibody studies reveal a relatively satisfying picture in the calf disease but not in the human disorder. It is known that colostrum is essential for the survival of the new-born calf and that it is the specific antibody content of the colostrum which is primarily responsible for the protection of those which survive. Breast-fed babies enjoy a resistance to *E. coli* infections not shared by those which are bottle fed. The infant mortality in Holland in 1953 was 28·4 per 1,000 under one year ; for the corresponding period in Belgium it was 43·3. It has been suggested that this difference is related to breast feeding ; in Holland most babies are breast fed whilst in Belgium fewer babies enjoy this privilege (Taylor, 1957). These observations cannot be related to a naturally acquired passive immunity. Babies acquire immunity from their mothers whilst still within the uterus ; calves acquire it after birth from the colostrum. Our lack of knowledge is revealed and we know little of what Dubos (1954) has described as the " physicochemical characteristics of the *in vivo* environment " which is so necessary if we are to understand " the pathogenic potentialities of a given micro-organism." Some of the puzzle may be clarified from our studies on bacterial antagonism ; This may be spoken of as studies on antibiotics. There is a similarity between the intestinal tract of animals treated with some antibiotics and the tract of young animals which have had little experience of their environmental bacterial flora. It was in 1925 that Smith & Orcutt reported on the relationship of *E. coli* to the intestinal tract of the calf. It was a quantitative one and small numbers of *E. coli* were present at all levels of the tract in normal calves ; there was an increase in numbers with a spread of the infection towards the duodenum in calves with an intestinal disturbance. Nearly 30 years later, in 1954, Anderson reported on the feeding of penicillin to pigs by which he induced in the intestinal tract a great rise in the number of coliform bacteria and a decrease in lactobacilli. Simultaneously the coliforms became more widespread in the intestinal canal and they could be isolated from the stomach, duodenum and anterior portion of the jejunum ; their presence appeared to be confined to the latter part of the jejunum in control pigs.

This similarity is more real than at first apparent because bacterial antagonism and bacterial competition occurs naturally in the throat, in the intestine and in the vagina of man and animals. The removal or suppression of a competitor enables one species to multiply excessively and ill effects are produced by bacteria which would be harmless if present in moderation. The ill effects of large numbers of coliform rods is reflected in the figures given by Blaxter & Wood (1953) for the total coliform count in the daily output of calf faeces. The figure for normal faeces is given as 11,800,000 and for diarrhoeal faeces as 290,700,000, a ratio of 1 to 24·6. The metabolic products of the bacteria are probably the main factors which are responsible for the initiation of the diarrhoea ; the greater the number the greater the effect and the greater the probability of invasion into blood and other tissues. It is interesting to note that many outbreaks of diarrhoea in young pigs to-day yield specific types of *E. coli* (Rees ; personal communication) ; one is tempted to relate this to the use of feeding-stuffs containing antibiotics. The object in bringing this to our notice is that lessons learnt in studies on the effect of antibiotics in the intestinal tract may help in understanding the balance and subsequent lack of balance, in the microbial flora of the intestinal canal of the young.

Johne's Disease

This is another condition in which it is important to distinguish between infection and disease. It appears as if the important factor, in so far as cattle are concerned, is the ability of the causal organism to multiply in the tissues. The difference is therefore between multiplication with disease and latent infection with little or no growth of bacteria.

The disease is one of calves ; all investigators agree that young calves under the age of 3 months are highly susceptible to infection. Under natural circumstances infection is probably established in early life and infected calves may become clinical cases or carriers without obvious signs. Animals of any age may become infected and excrete the organism, but the bulk of the evidence points to the high degree of susceptibility of

the calf to the disease. It is also agreed that the bacillus of Johne's disease may be found in the mesenteric lymph nodes of a comparatively high proportion of apparently normal cattle. Infection with this bacillus is therefore not the same as Johne's disease. It seems as if the conditions found in the young calf are such whereby this micro-organism can multiply to such an extent that clinical symptoms and lesions become obvious. In adult cattle the organism is limited in its activity ; the carrier state with or without excretion of the organism is the extent to which it is allowed.

Little experimental work appears to have been recorded on the endo-toxins which are inherent in the bacillus of Johne's disease. Many experiments have been made with tubercle bacilli and the tissue responses induced in an animal host vary according to the chemical fraction which has been prepared. Tubercle bacilli are able to induce a necrosis and this necrosis may ensue when the infected tissue contains a sufficiently large number of bacilli ; it matters not whether they are virulent or non-virulent. It therefore seems as if all mammalian tubercle bacilli, whether virulent or avirulent, possess similar toxic properties. It is the rate of multiplication and the ability to multiply which is the main determinant factor in the production of tuberculosis. It is this which differentiates the disease process from infection.

Except in sheep, which is another puzzle, Johne's bacilli do not cause necrosis ; the specific tissue response is in other respects similar to that induced by tubercle bacilli. The stimulus provided by this micro-organism produces cellular proliferation and the endothelioid cell is the typical cell in tuberculosis and in Johne's disease. It seems as if weakened toxic products of tubercle bacilli are comparable and have similar effects to the toxic products of Johne's bacillus. It may be assumed therefore that the toxic products of *Myco. johnei* are responsible for the specific cellular changes. The proliferation of the cells of the host occurs when sufficient bacteria are present ; the picture therefore is similar to some we have already met in so far as the determinant factor is concerned. This is the ability of the bacterium to multiply in the tissues ; this decides whether the result in the host is infection alone or disease.

Myco. johnei grows slowly under artificial conditions and the disease with which it is associated is a chronic one with a prolonged period of incubation. These facts are probably related to each other.

The problems awaiting solution differ in some respects from those concerning the acute disorders in babies and calves associated with *E. coli*. In the latter, the bacteria multiply rapidly in the tissues of the baby or calf. In Johne's disease, it is obvious that the tissues of the calf are suitable for the establishment of the causal bacteria. Are the tissues of the calf the environment suited to the growth of the bacteria or is there a latent period of a year or two and then multiplication of the bacteria ? This knowledge is necessary before one asks questions as to the availability of specific bacterial nutrients in the calf tissues or as to the possibility of inhibiting factors in the tissues of adults. The nutritional status of the host has interested some investigators and a few field observations have been made which suggest this influence in the onset of the disease in cattle. The solution of some of the problems envisaged will help in the control of the disorders of youth whether they be of man or animals.

The main problem concerns the environment which enables certain infective agents to multiply ; the mechanisms of multiplication interest the biochemist and bacteriologist. The problem concerns mainly the endemic diseases and the reasons for their resurgence. Latent infection in bacterial and virus infections is common and recognised ; bacterial mutation exists and virus mutation is probable. The instability and variability of the infective agents and of the animal hosts complicate their relationships. Some of the experiments made with animals born and bred under " germ free " conditions reduce the variables. The suppression of some species of bacteria by the administration of antibiotics to experimental animals may reduce other complicating factors. Neither approach is ideal because of the artificial conditions which are produced ; both may give guides towards the truth. The study involving the significance of the age of the host in infective diseases is one small part of the subject of epidemiology, a study which knows no end.

Moving a vote of thanks to the author of the paper, the Chairman, Professor W. I. B. Beveridge, said they had expected a first-rate address from Professor Lovell and he had fully maintained his reputation. He had shown how people must reorientate some of their thinking about infectious diseases and then relate these principles to real life problems.

The vote of thanks was carried by acclamation.

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XUM

Studies in Scrapie

BY

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THERE is a mystery about scrapie that makes it an unpopular subject for research; its study can be a chastening experience. The condition has defied solution so persistently that perhaps it should be classified as a disease extraordinary. For not only is the pathology of scrapie unconvincing, using the accepted criteria of pathological significance, but the clinical signs are prolonged and obscure. Moreover material used for its experimental transmission can withstand the most extraordinary insults and the "incubation period" is believed to vary from a few months to over a year.

Although the present anxiety over scrapie arises particularly from its effect on British sheep exports, the scientific interest lies in the possibility that in its solution a new concept of the genesis of disease may arise.

What is the present position of research into this disease?

The transmission from sheep to sheep as reported by Gordon (1946) and Wilson, Anderson & Smith (1950), has frequently been criticised on account of the possibility of previous contamination of pasture and the difficulty in obtaining disease-free stock for inoculation. The successful transmission of a scrapie-like condition to goats however, using material from sheep affected with the disease (Pattison, 1957) puts the earlier work in a more favourable light, especially as a natural case of scrapie in a goat has only been reported previously on a single occasion (Chelle, 1942).

Although few shepherds experienced with scrapie have difficulty in recognising the disease there is still no adequate clinical definition of the syndrome. This problem is also complicated by the absence of generally accepted histopathological changes. If adequate clinical and pathological criteria of the disease could be established, the question of control and aetiology may well be simplified.

The purpose of this paper is to mention some of the clinical signs of scrapie that are believed to be important in its diagnosis, and to provide evidence that the cytological changes in the nerve cells are associated with the disease and are of significance.

The report is based on the study of over 20 cases of scrapie under hospital conditions as well as observations made in the field. Through the kindness of Dr. D. R. Wilson and Mr. I. H. Pattison respectively the series of affected animals includes two sheep and two goats to which the disease was transmitted by inoculation. Methods used in the investigation will be described later. Details of the animals used will be provided at the Congress.

Clinical Signs

Until a serological or similar test is evolved, the diagnosis of scrapie in the living animal must depend upon the observation of clinical manifestations. In recent articles by Bosanquet, Daniel & Parry (1956a) and by Parry (1957) the symptomatology of the condition has been reviewed: I therefore only propose to elaborate a few aspects that may contribute towards establishing the identity of the disease.

As a prelude to observations in the field I was fortunate in obtaining from Dr. D. R. Wilson the two sheep to which the disease was transmitted by inoculation. One of these animals was examined over a period of six months and the other for one month. It is believed that these two animals, maintained under experimental conditions, afforded a useful template with which subsequent field observations could be compared, as the risk of intercurrent disease was minimised. The clinical signs of cases of scrapie obtained later from affected farms were strikingly similar to the manifestations of the two earlier cases: differences were generally of degree rather than of kind.

Although not necessarily the earliest sign of scrapie one of the most important is the apparent irritation that induces the animal to rub itself relentlessly, nibble the skin and tear out the wool: the areas denuded of fleece are usually bilaterally symmetrical. This behaviour, in my experience, has always preceded detectable alterations of gait, often by several months. The nibbling response can be elicited by rubbing wool-covered areas with deep or light pressure; sometimes touching the fleece is sufficient stimulus to elicit the reaction. Nibbling may also be aroused by using nocuous stimuli such as repeated pin-prick and touching with hot and cold objects, stimuli that in the normal animal result in withdrawal and escape. When an affected sheep is disturbed or excited the nibbling response is difficult or impossible to elicit. This absence of the reaction, which may have important consequences in the diagnosis of the disease, has also been noticed when an animal has been introduced to an abnormal environment. Thus, one affected sheep, observed to have had the response when originally examined on the farm, did not show the response when observed for a month under hospital conditions. The conclusion must be that this nibbling response can be influenced by external factors and its absence cannot justify the designation of a non-irritative form of scrapie.

Two kinds of tremor have been found in affected sheep; the one an intermittent nodding or jerking of

the head and the other a violent inco-ordinated jerking of the limbs and head seen especially when an animal is evading capture. This behaviour is particularly evident in sheep that show other signs of hyperexitability. Fasciculation of superficial muscles has also been observed and this has been confirmed electromyographically.

When the first signs of scrapie are present, abnormal locomotion is not usually apparent. With the progress of the disease the hind legs are usually the first to show abnormalities, exhibiting a shortening of the excursion of the step, with the limb moving as a whole rather than flexing at the hock. There is adduction of the hind legs during their protraction and an abduction during retraction. The movement between the fore and hind legs becomes inco-ordinate and there is weakness and imbalance of the hindquarters. The sheep may be slow to correct abnormal posture of the hind legs as if the animal is not conscious of the spatial position of the limbs. Finally the animal appears too weak to walk, although actual paralysis has not been observed. Deep and superficial reflexes are normal although in the ultimate stages of the disease there may be an increase of resistance to passive movement, especially in the hind legs.

Positional nystagmus (nystagmus elicited by tilting the head sideways) has been observed in 10 out of 25 affected animals, including one goat. This nystagmus has occurred in the absence of lesions in the membranous labyrinth and in the absence of evidence of ketosis. Experiments were performed using an adaptation of the Caloric or Bárány test to determine whether the nystagmus produced by stimulation of the labyrinth was different in early cases of scrapie from that obtained in normal sheep. A caloric response was obtained on over 400 occasions in 14 normal and two affected sheep using water at a temperature of 30°C; nystagmus was not elicited with water at 44°C. No differences were observed in the duration of the response between affected and normal sheep except when positional nystagmus was already present in diseased animals, when the duration was longer. The possibility of using the Caloric test as an aid to the early diagnosis of scrapie was therefore abandoned.

Other manifestations of scrapie that have been observed include inability to swallow food or water despite normal prehension, regurgitation of ruminal contents, loss of bleating and blindness.

Because Feldberg & Sherwood (1954b) produced scratching and apparent irritation in cats by the injection of drugs into the lateral ventricle, similar experiments were performed on five normal sheep in an attempt to mimic the rubbing of scrapie. Cannulae were implanted permanently into the lateral ventricle of these animals and the following agents were injected: eserine sulphate, prostigmine, carbachol, nicotine hydrogen tartrate, acetyl choline chloride, D.F.P., morphine sulphate, adrenaline and noradrenaline bitartrate, atropine sulphate and histamine sulphate. After the injection of these agents there were often alterations of the animals' behaviour, usually manifested by motor abnormalities. Following the administration of eserine the sheep occasionally kicked the side of the face with the hind leg, but apart from this there were no signs of rubbing or irritation. Attempts to reproduce the intense apparent irritation as observed in scrapie by these methods therefore failed.

Histopathology

1. *Myopathy*

Scrapie has frequently been the subject of controversy as witnessed by the contradicting opinions expressed by McFadyean (1918) and McGowan (1918) concerning the rôle of sarcosporidia in its aetiology. It is therefore interesting that the hypothesis that scrapie is essentially a disease of muscles has once again arisen (Bosanquet, Daniel & Parry 1956a; Parry, 1957); for these authors discovered lesions of myopathy in sheep affected with scrapie which they believed could go a long way in explaining the clinical signs of the condition. On the other hand few data were provided concerning the quantitative distribution of the lesions in affected animals and the lesions were also described in sheep affected with disease other than scrapie. These authors also concluded that the vacuolation of neurones, so frequently described in the literature as being associated with scrapie, is of no significance.

Prior to the papers concerning this myopathy I had not detected these changes in the muscles and this earlier investigation had included a histochemical study of the motor end plates (which appeared to be normal). Subsequently a careful search has been made for myopathy in seven sheep and two goats affected with scrapie and three muscles from three animals have been found to be involved.

In view of these results it seems improbable that myopathic changes in muscle are the essential pathological lesion of scrapie. It is possible that myopathy is widespread in the sheep population of this country and that it can co-exist with scrapie.

2. *Is vacuolation an artifact?*

The reluctance to accept the vacuolation of neurones to be of importance in scrapie is based on two factors; (1) that vacuolation can occur in the C.N.S. as the result of anoxia (Lindenberg, 1956) and improper histological treatment of tissue and (2) that there is little convincing evidence that vacuolation in scrapie is accompanied by glial reaction. Evidence will now be presented to show that cytologically these neurones are abnormal and that their occurrence is associated with scrapie.

Vacuolated nerve cells, in scrapie, are found in the spinal cord, medulla, pons and midbrain. Individual vacuoles are intracytoplasmic and are up to 80 to 100μ in diameter, see Fig. 1; sometimes there are two or more vacuoles in a single neurone and occasionally the vacuolation extends down into the emerging nerve fibre, Fig. 2. No morphological differences have been demonstrated in the vacuolation after using the following different methods of fixation: 10 per cent. formalin; 2 per cent., 5 per cent., 10 per cent. and 30 per cent. formol-saline; 10 per cent. formol-saline intravitally; formol-ammonium bromide; formol-acetic-alcohol; Bouin's;

Carnoy's; Regaud's and Zenker's. The vacuoles are also equally apparent in paraffin and celloidin embedded material as well as in frozen sections, see Figs. 1, 3 and 4.

3. *Nature of the intravacuolar material*

Inside the vacuoles eosinophilic material (originally described by Holman & Pattison, 1943) is often found, see Fig. 5. This material is usually spheroidal; individual bodies measure from 2 to 12μ in diameter, and often contain small deeply staining eosinophilic granules. The bodies occur in vacuoles in the efferent nerve fibre Fig. 2 and occasionally in the cytoplasm of apparently non-vacuolated neurones, Fig. 6.

The intravacuolar bodies have been studied histochemically (Palmer, 1957) but the results have been largely negative. The bodies did not stain with the periodic acid-Schiff reaction, the Feulgen reaction, the benzidine reaction, the neutral fat stain "Fettrot" (Ciba), methyl green-pyronin, permanganate-paraldehyde-fuchsin, or with Methasol fast blue 2G. There was, however, a moderately positive coupled tetrazonium reaction, Fig. 7, which suggests that the bodies contain protein.

4. *Is there a glial reaction*?

In regions where profuse vacuolation is found, the nerve cells are in various stages of distortion and other neuro-pathological abnormalities could legitimately be expected.

I have been unable to establish that there are significant changes in the glial elements despite the use of specific glial stains. Undoubtedly the proportion of the different elements of the glial population of normal sheep varies from region to region of the brain, and so a study of the glia must be adequately controlled. But even in these circumstances no constant changes have been detected. In passing, one feature of the protoplasmic astrocyte in sheep is worth comment; surrounding the nuclei of the cells, there are a number of small granules, Fig. 8. The granules stain intensely with thionin, permanganate-paraldehyde-fuchsin and with the periodic acid-Schiff and coupled tetrazonium reactions. In an investigation of these granules in the inferior olive of 27 normal and diseased sheep (ranging in age from a full-term foetus to 11 years) it was found that the granules occurred in both groups of animals, but they were rarely evident before about the sixth month of life. It was concluded that these granules are a normal feature of the protoplasmic astrocyte in sheep.

5. *Extracellular material*

In areas of intense vacuolation round and oval extracellular bodies, up to about 30μ in diameter, are often found, Fig. 9. This material must not be confused with amorphous eosinophilic material frequently situated in the lateral cuneate nucleus of normal as well as diseased sheep. The extracellular round bodies sometimes stain positively with the periodic acid-Schiff reaction and frequently they appear to be surrounded by a translucent halo. The bodies are often situated in close proximity to nerve cells. First impressions suggest that the bodies are degenerating axons, but attempts to substantiate this idea have failed. Although these bodies are argyrophilic, using the following techniques, Holmes, Nauta & Ryan and Gros-Bielschowsky, they have been shown to be quite independent of the axons, the latter presenting no apparent abnormality. Moreover, there is usually no evidence of a myelin sheath surrounding these bodies. At present their identity is unknown.

6. *Other neuropathological changes*

No constant abnormality has been found in the blood vessels, the meninges or in the choroid plexus. Perivascular cuffing quite often occurs in the brains of both healthy and affected sheep. Breakdown of myelin has only occasionally been seen.

7. *Neuro-anatomical distribution of vacuolated neurones*

The distribution of vacuolated neurones in the brains of sheep affected with scrapie has also been the subject of investigation. Owing to restrictions of space, it is impossible to provide full details of these experiments, which were based on the serial sections of three normal and four affected brains. Vacuolated neurones were found in the spinal cord, medulla, roof nuclei of the cerebellum, pons and mid-brain of affected sheep, but not in the cortex of either cerebrum or cerebellum. In the ventro-medial nucleus of the hypothalamus and in the mammillary nucleus, intracytoplasmic vacuolation occurred, Fig. 10, but the character of this vacuolation was different from that at more caudal levels, in that the former rarely exceeded 20μ in diameter, did not contain eosinophilic bodies and the neurones did not show signs of degeneration. As vacuolation in the hypothalumus has also been reported in normal animals, *e.g.*, in the dog (Jewell, 1953), it was concluded that this vacuolation was not the same as the vacuoles associated with scrapie.

In scrapie, when vacuolation is intense, it affects the neurones of a paired nucleus, for instance the lateral cuneate, to approximately the same extent on both sides. The bilateral disposition is characteristic and may be of importance in determining the possible causes of the vacuolation. Some groups of nuclei in the medulla and pons rarely contain vacuolated cells despite there being many affected neurones in adjacent areas. The regions that appear to be almost immune to vacuolation include the inferior olive, the large cells of the nucleus ambiguus and the nucleus of the hypoglossal. There is no apparent reason, anatomical, cytological or physiological, why these neurones should not be affected.

Neuro-anatomically the following regions generally show the most severe vacuolation; the lateral cuneate nucleus (LCN), the lateral caudal nucleus of the reticular formation (LCD), the interfascicular nucleus of the hypoglossal, the pontine and medullary reticular formation and the papillioform nucleus, (see Meessen & Olszewski, 1949 for a description of these regions in the rabbit). These results on the distribution of the vacuolation are in general accord with those of Holman & Pattison, 1943.

TABLE I

Class	Number of sheep	Number of sections	Total number of vacuolated neurones	Mean vacuolated neurones per section	Range vacuolated neurones per section	Probable standard error of mean
Scrapie	19	190	3,492	18·4	0–93	1·73
Nervous diseases not scrapie	13	254	7	<1	0–1	<1
Normal	16	324	10	<1	0–1	<1

8. *Relation of vacuolated nerve cells to animals affected with scrapie*

In order to determine whether vacuolated neurones occur more commonly in sheep affected with scrapie or whether indeed they exist in normal sheep or in sheep affected with other nervous diseases, the following investigation was carried out. Blocks of medulla, selected to include the lateral cuneate or the lateral caudal nucleus, or both, were obtained from normal and diseased animals of different ages, breeds and sexes. The area of medulla concerned is shown in Fig. 11. Of the animals used, 19 showed clinical signs of scrapie, 13 were affected with nervous disease other than scrapie (including listerellosis, coenuriasis, meningitis, tetanus and compression lesions of the cord) and 16 were clinically healthy animals. Sections of the medulla varied in thickness from 7 to 12μ according to whether the material was embedded in paraffin or celloidin respectively. The thicker the section, the more chance there was of finding vacuolated neurones, because of the greater number of nerve cells present to examine. However, the bias was weighted in favour of the control material.

The results of these experiments are given in Tables I and II. Vacuolated neurones occurred more abundantly in the material from sheep affected with scrapie than in either of the two control groups. The frequency distribution of vacuolated neurones for affected animals is not quite normal, but the difference between means for the control and healthy animals is so large that this is probably of little consequence. Where vacuolation occurred in the control medullas, it was found (with one exception) entirely in the dorsal nucleus of the vagus, whereas in most cases of scrapie vacuolation was found in many other nuclear masses. In the control material intravacuolar bodies were found on a single occasion.

Vacuolated neurones in the medulla of goats to which a scrapie-like condition was produced after the injection of material from affected sheep was reported by Pattison (1957). Mr. Pattison has kindly supplied me with two clinical cases of the condition. The character of the vacuolation in the goats is similar to that found in sheep; both intravacuolar bodies and extracellular bodies (see earlier) occur. Data of the numbers of vacuolated nerve cells observed in these goats is provided in Table III. Numbers of vacuolated neurones in normal goats were reported by Pattison (1957).

9. *The nature of vacuolated nerve cells in species other than sheep*

The character of the vacuolation that occurs in scrapie was compared with the vacuolation of nerve cells found in the C.N.S. of animals other than sheep and goats affected with nervous diseases. In these experiments the brains of over 60 animals (cattle, pigs, dogs, cats, rabbits, mice and poultry) were examined histologically, using sections stained with H. & E. at levels caudal to the thalamus. Vacuolation was found in this material, particularly in the regions of brain adjacent to neoplasms, in animals in which there was probably anoxia during the terminal phases of life, and in Purkinje cells in avian encephalomalacia. The vacuolation in these cases was usually around the margin of the cell and was foamy and polylocular; the vacuoles did not extend down the efferent nerve fibres and intravacuolar bodies were not observed. Morphologically these vacuoles were quite distinct from those seen in scrapie.

TABLE II
VARIANCE ANALYSIS TABLE, SHEEP AFFECTED WITH SCRAPIE

Source	Sum of squares	Degrees of freedom	Mean squares	Variance ratio	p
Between sheep	98,581	18	4,979	180	< <0·001
Between sections for a sheep	4,728	171	27·65		
Total	103,309	189	546		

Standard deviation 23·4.
Mean 18·4 ± 1·73 vacuolated neurones per section.

Discussion

Clinical signs

Clinical signs common both to naturally occurring cases of scrapie and to sheep to which the disease was artificially transmitted, suggest that both groups of animals were affected with the same syndrome.

Manifestation of scrapie believed to be important

TABLE III
VACUOLATION IN TWO GOATS AFFECTED WITH SCRAPIE

Goat	Number of sections	Total number of vacuolated neurones	Range of vacuolated neurones per section
1	10	733	62–89
2	10	103	4–18

are, apparent intense irritation, tremor, hyperexcitability, abnormal gait, positional nystagmus and debility.

There is evidence that some of the signs can be influenced by external factors, *e.g.*, the inhibition of the nibbling response by environmental factors; no doubt intercurrent affections can also lead to the superimposition of other clinical features upon the basic pattern. Scrapie appears to be a syndrome in which there can be clinical signs of varying severity although the nature of the manifestations are essentially of the same kind.

Clinically the tremor and hyperexcitability suggests that scrapie is a nervous disease, although the early changes of behaviour can occur without intense vacuolation of the neurones. So far there has been no adequate neuro-anatomical explanation of these early abnormalities; perhaps the inability to explain the clinical signs of tetanus histopathologically represents a comparable problem.

This difficulty in accounting for the nervous signs of scrapie reflects on the inherent limitations in attempting neurological examination of animals. Reliable information cannot be obtained of the nature of slightly deficient or abnormal sensation; proprioception cannot be assessed. If scrapie were a disease affecting man, this matter might now be resolved.

Histopathology

1. *Significance of vacuolated neurones*

Experiments designed to test the effects of different methods of fixation and of embedding upon the vacuolation of neurones have shown the vacuoles to be present under all these conditions. The morphology of the vacuolation was identical in all these separate investigations. The possibility of vacuolation being an artifact is therefore remote.

The significance of vacuolation in scrapie depends on two considerations, the occurrence of vacuolated nerve cells in animals affected with the disease and the evidence of cytological damage. Evidence has been given to show that vacuolation is found in sheep naturally affected with scrapie and in sheep to which the disease has been transmitted. Moreover, the occurrence of similar vacuolation in goats inoculated with material from affected sheep supports the belief that vacuolation is an important concomitant of the disease.

The cytological changes in the nerve cells consist of a progressive vacuolation both in the cytoplasm and in the efferent nerve fibre and the production of eosinophilic vacuolar contents. These changes indicate severe and perhaps chronic damage to the neurone. The nature of the process does not, however, conform to the usual pattern of nerve cell degeneration, as described in other nervous conditions in man or animals. An exactly comparable process does not appear to have been described. In 1955 Müller & Walter reported vacuolated nerve cells in sympathetic ganglia removed from hypertensive patients. These vacuoles were often empty, but some were filled with a crumbly, thread-like material that stained with acid dyes. Neurones containing vacuoles have also been found in the medulla and cord of patients suffering from acute porphyria (Gibson & Goldberg, 1956) but in these cases no intravacuolar contents were described.

In the animals used as controls in the present experiments, a few vacuolated nerve cells were found. See Table I. Zlotnik & Rennie (1957), however, reported vacuolated neurones in about 70 per cent. of medullas obtained from 57 apparently healthy sheep (mostly Cheviots). These workers examined 180 sections from each medulla. In some brains only one vacuolated nerve cell was found while in others there was one or more affected neurone per section: the maximum intensity was seven vacuolated nerve cells in a section. Zlotnik & Rennie explained the occurrence of vacuolated neurones in healthy sheep as follows: (1) their sheep were incubating scrapie; (2) the sheep were affected with a non-clinical form of the disease or (3) vacuolation is not connected with scrapie.

In some of the affected sheep used in the present investigation as many as 90 vacuolated neurones were present in a single section and it is unlikely that such intensive vacuolation can be compatible with normality. Moreover, on cytological evidence, there is much to suggest that vacuolation of a nerve cell causes profound dysfunction and such a cell cannot be regarded as normal.

2. *Distribution of vacuolated neurones*

The distribution of vacuolated neurones in the C.N.S. of animals affected with scrapie is of interest in two aspects. If intense vacuolation is accepted as a satisfactory confirmatory test for the disease, the region where vacuolated neurones are most likely to be found is important. Blocks prepared from the caudal part of the medulla including lateral cuneate nucleus and lateral caudal part of the reticular formation, afford one of the best sites for finding vacuolation. This region also has the advantage that it is easy to prepare histologically.

The second reason why the distribution of affected neurones may be important is that the distribution may be related to the cause of the vacuolation. It would be interesting to know why the vacuoles are confined to areas caudal to the thalamus and why there is a bilateral equality in their distribution in severely affected brains, and yet in moderately affected material the distribution is haphazard. Neuroanatomically the gross distribution is similar to the distribution of suppurative foci that have been observed in two cases of ovine listerellosis. The bilateral disposition on the other hand is similar to the bilateral distribution of lesions in the basal ganglia found in toxic conditions such as carbon monoxide poisoning. If vacuolation in scrapie results from a systemic metabolic disturbance, in which special groups of neurones become the targets, why is it that on occasions such selective vacuolation is distributed sparingly and haphazardly?

3. *Nature of the intravacuolar and extracellular material*

In this investigation the presence of material inside a proportion of the vacuoles has been a regular

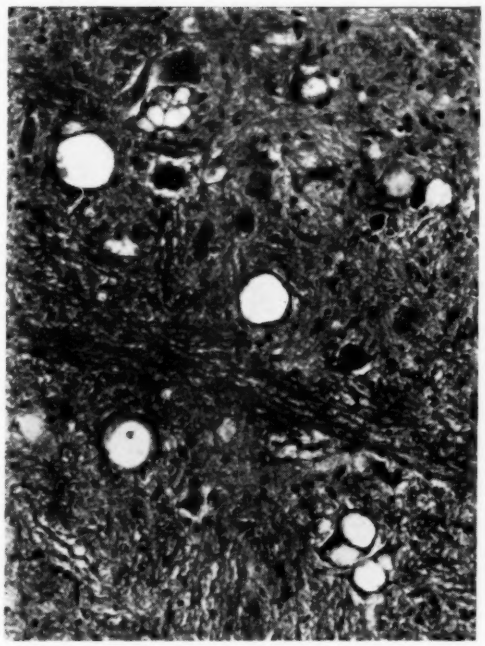

FIG. 1.—Vacuolated neurones from sheep affected with scrapie. H. & E., celloidin, × 200.

FIG. 2.—Vacuoles with eosinophilic contents in efferent nerve fibre, from sheep affected with scrapie. H. & E., celloidin, × 650.

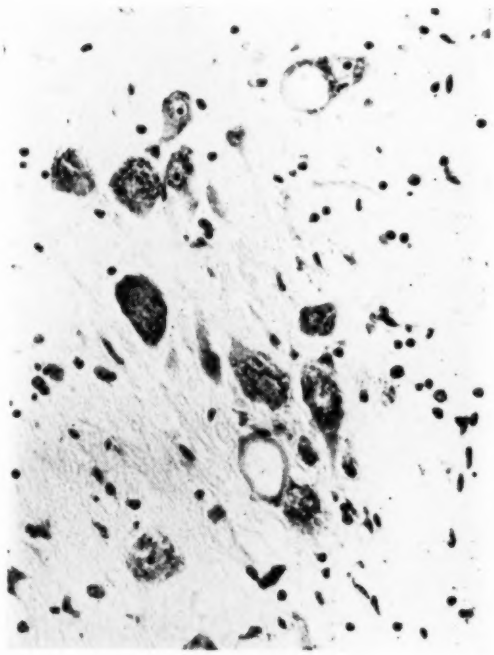

FIG. 3.—Vacuolated nerve cells from sheep affected with scrapie, to show Nissl substance. Thionin, paraffin, × 300.

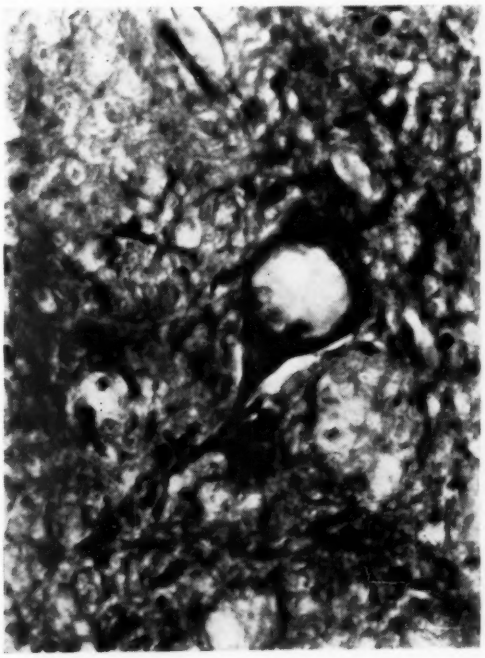

FIG. 4.—Vacuolated neurone from sheep affected with scrapie. H. & E., frozen, × 480.

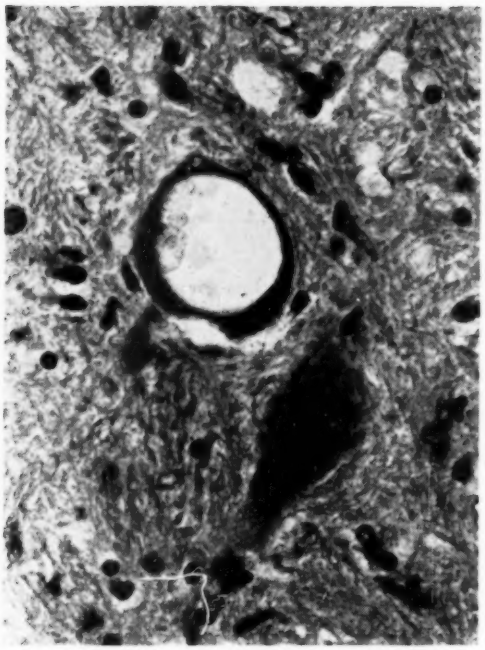

FIG. 5.—Bodies inside vacuole, from affected sheep. H. & phloxine, celloidin, × 670.

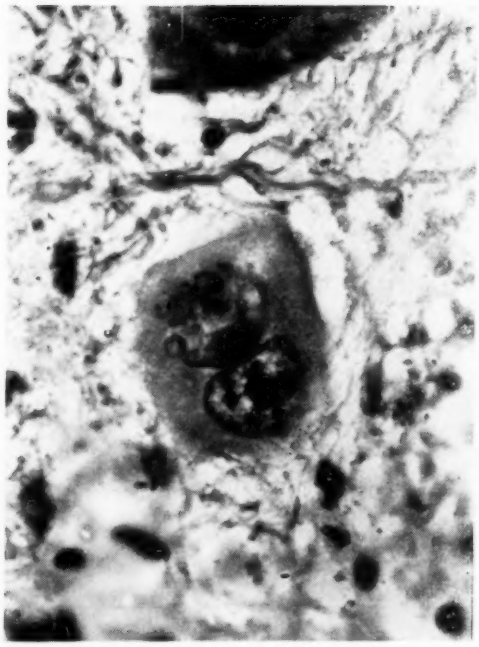

FIG. 6.—Bodies in cytoplasm of apparently non-vacuolated neurone from sheep affected with scrapie. H. & E., celloidin, × 900.

FIG. 7.—Bodies in vacuole, stained with the coupled tetrazonium reaction, celloidin, × 600.

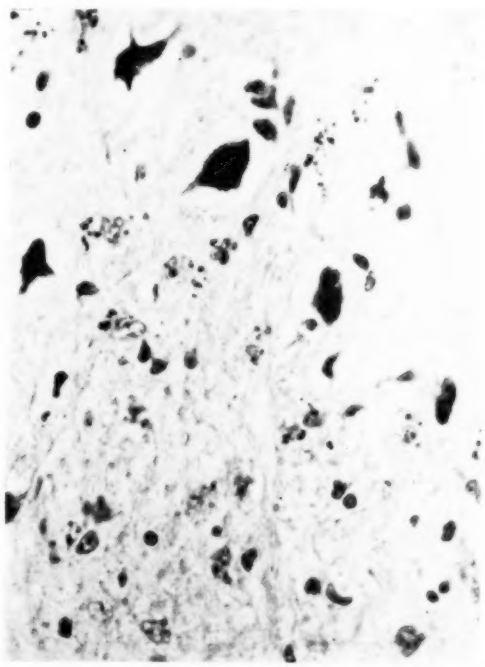

FIG. 8.—Granules surrounding nuclei of astrocytes found in both normal and diseased sheep. Machiovello, paraffin, × 550.

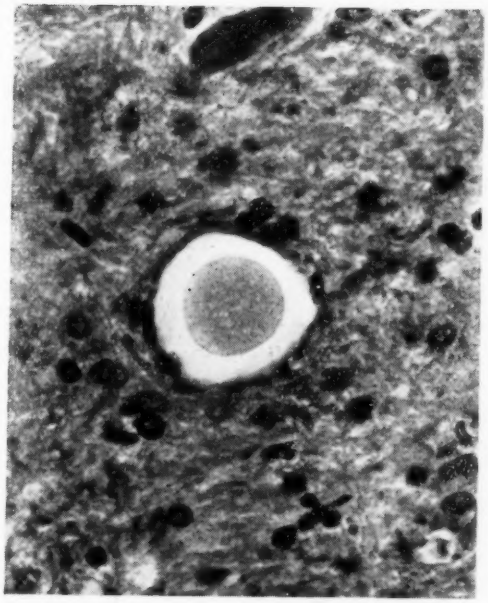

FIG. 9.—Extracellular round body, found in areas of intense vacuolation. H. & E., celloidin, × 650.

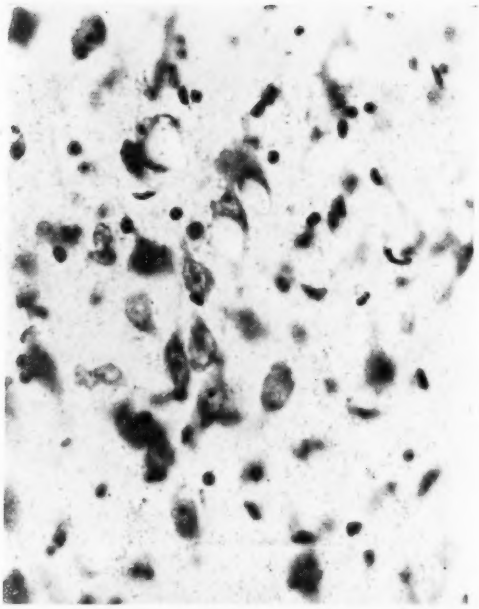

FIG. 10.—Vacuolated neurones in the ventro-medial nucleus of the hypothalamus from sheep affected with scrapie. Thionin, celloidin, × 425.

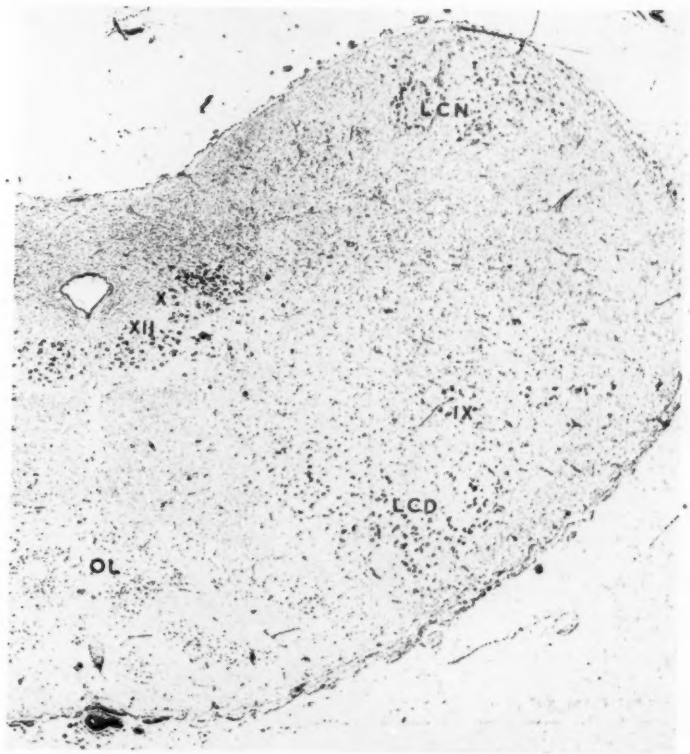

FIG. 11.—Region in medulla of sheep where vacuolated neurones are frequently found. Thionin, celloidin, × 16. Lateral cuneate nucleus (LCN), dorsal nucleus of the vagus (X), nucleus of the hypoglossal (XII), nucleus ambiguus (IX), lateral caudal nucleus of the reticular formation (LCD) and inferior olive (OL).

XUM

observation and occasionally the small bodies have also been found within the cytoplasm of non-vacuolated cells. Similar material has not been found in other kinds of vacuolation in the nerve cells of other species and it is possible that this material is characteristic of the vacuolation associated with scrapie.

Morphologically the material in the vacuoles usually appears as separate bodies with discrete contour. The bodies first appear to form in the cytoplasm of the neurone, the nucleus of the cell sometimes being eccentrically placed. As vacuolation proceeds the bodies increase in size, remaining in the vacuole. They appear to be associated with the process of vacuolation and could equally well be inclusion bodies or simply products of cellular degeneration. The inability to demonstrate nucleic acid in the bodies suggests that they are not virus inclusions, but these negative results may be associated with the limitations of the histochemical methods employed. If, on the other hand, these bodies are not inclusions they could arise from degeneration of the cytoplasm or an over-production of axoplasm, the material assuming a spheroidal shape because of the physical conditions within the cell.

Zlotnik (1957) reported eosinophilic bodies in the cytoplasm of neurones from both healthy and affected sheep. In the present investigation this intracytoplasmic material was only found, infrequently, in the neurones of affected animals. Zlotnik also described granules, staining positively with the periodic acid-Schiff reaction, in the nerve cells from healthy sheep. These granules have been observed in the present experiments, and were reported by Dixon & Herbertson (1950a and b) in neurones of man, the rat and the rabbit.

The occurrence of round extracellular bodies in areas of intense vacuolation poses yet another problem. On the grounds of specific staining methods there is no evidence that these bodies are degenerating axons and this is supported by the fact that they rarely occur in the white matter. They are also unlikely to be the end products of cytoplasmic degeneration as in the final stages of vacuolation the Nissl substance constitutes a narrow rind of tissue around the vacuole. The bodies could nave a completely exogenous origin.

4. *Neuroglia*

The absence of a reaction by the glial cells presents a difficulty as the glia are usually a reliable indicator of a neuropathological process. However, perhaps the neuronal damage in scrapie is not sufficiently acute to instigate a microglial reaction. The process of astrocytic proliferation is known to depend on the previous injury to the astrocytic cells themselves (Hicks, 1947) and there is no evidence that such damage occurs in scrapie.

The absence from brains of animals affected with scrapie of inflammatory reaction common to virus encephalitides does not preclude the possibility that scrapie is caused by a virus. All these other encephalitides have an acute clinical course and are accompanied by acute inflammatory changes in the nervous system. Scrapie, on the other hand, is a chronic clinical condition and acute inflammatory changes in the nervous system are not necessarily to be expected.

5. *Myopathy*

The inability to demonstrate widespread myopathic lesions in animals affected with scrapie in these experiments poses two questions: (a) whether there is evidence that myopathy is the essential lesion in scrapie and (b) whether the myopathic lesions are so small that they cannot be seen with the naked eye. If the latter is true, then their detection will depend on the microscopical examination of all the musculature in the body, which will present a formidable task. On the evidence of investigations included in this report it appears that myopathy exists in sheep and goats but it is unlikely to be responsible for the complicated nervous manifestations of scrapie.

In conclusion, there are several possible explanations of the aetiology of scrapie. The agent could be a virus with the most extraordinary resistance to chemical and physical destruction or it could be a chemical agent that can trigger off an hereditary or acquired disposition to scrapie. This latter process might involve the production of an anti-enzyme in the host body.

Summary

1. Over 20 cases of scrapie were examined, including two sheep and two goats to which the disease was transmitted.

2. The clinical signs of scrapie are briefly described; the nibbling response can be influenced by external factors.

3. It is suggested that the various signs observed in scrapie are probably manifestations of the same syndrome, differing in degree rather than in character.

4. Attempts to produce signs of itching in normal sheep by the injection of drugs into the lateral ventricle of normal sheep are described.

5. The nature of the vacuolation of neurones in scrapie is described. Evidence is given that vacuolation is not an artifact.

6. The intensity of vacuolated neurones in the medulla of 19 animals affected with scrapie was compared with the intensity found in the same region in 13 sheep affected with other nervous diseases and 16 apparently healthy sheep.

7. Early signs of scrapie can occur without intense vacuolation.

8. Extracellular round bodies were found in regions where there was intense vacuolation.

9. Small granules have been found surrounding astrocytic nuclei in brains from both normal and abnormal sheep. These granules are rarely found before the sheep is six months old.

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Hospital, Queen Square, London, for advice and for providing facilities. The intraventricular experiments were carried out with Dr. W. Feldberg at the National Institute for Medical Research, London. Dr. J. T. Abrams kindly assisted me with the presentation of the data. I am grateful for the technical assistance of Mr. I. K. Gauld; Mr. J. A. Mills was responsible for the photomicrographs.

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THE SPEAKER'S INTRODUCTION

Mr. Palmer said there was a tendency for both farmers and research workers to keep too much information about scrapie to themselves. In his paper he had confined his remarks to the clinical manifestations of the disease and to the neuropathology. He expressed the hope that measures of control would be discussed by Dr. Gordon and the nature of the transmissible agent by a representative from Moredun.

The clinical signs of scrapie could be influenced by external factors, but he believed there was insufficient evidence at present to justify dividing the clinical manifestations into several types. Forms of the disease were different in degree rather than in kind.

He did not wish to detract in any way from the importance of the discovery by Mr. Parry and his colleagues that there was a widespread myopathy occurring in the sheep population of this country. He had, however, been unable to confirm that this myopathy had any direct relationship with scrapie.

With regard to neuropathology, he hoped that he had succeeded in demonstrating that vacuolation was a serious cellular lesion. Signs of scrapie could undoubtedly occur without severe vacuolation in the medulla. Where intense vacuolation had occurred, it had only been found in tissue from affected sheep. Another interesting feature of vacuolation was that where it occurred it was usually bilaterally symmetrical involving certain specific nuclear masses in the brain.

Mr. Palmer concluded his opening remarks with an exhibition of a film demonstrating the clinical manifestation of the disease.

The Opener

Dr. W. S. Gordon, in opening the discussion said: "I like the two opening paragraphs of Mr. Palmer's paper because they express, so effectively, the present position in the investigation of the enigmatic disease of sheep known as scrapie. While it may be an unpopular subject for research, it is a most intriguing one. Regrettably, it does not hold out hope of easy victory because it is a disease that does not behave according to the accepted rules of pathology, virology or immunology. Its study, as Mr. Palmer says, can be a chastening experience, as I found to my discomfiture in the years between 1936 and 1939 when I not only felt chastened, but was castigated, by the appearance of scrapie in sheep inoculated with a certain batch of louping-ill vaccine which I had made. However, although this misfortune was responsible for the introduction of scrapie to certain farms where the disease had not been known before, it provided a substantial clue that scrapie was probably a transmissible disease. At the same time two Frenchmen, Cuillé & Chelle (1936) reported the transmission of scrapie to 2 ewes by injection of nerve tissue from animals naturally affected with the disease. I reported this occurrence (Gordon, Brownlee, & Wilson, 1939) at the International Congress of Microbiology, in New York, and again (Gordon 1946) at the B.V.A. Annual Congress, and it has also been reported by Greig (1950).

"Mr. Palmer set out with the intention of studying the clinical signs of scrapie and of examining the cytological changes in the nerve cells of the central nervous system to determine their significance in relation to the disease. He has done a thorough and painstaking piece of work and I am not at controversy with any of his main findings.

"I need not dwell on the clinical signs of this disease which have been so perfectly depicted in the film Mr. Palmer has shown. As you have seen there are two main presenting symptoms, that of a relentless sensation of itch which the animal becomes addicted to alleviating, and a varying degree of disorder of function of the nervous system characterised by inco-ordination of gait, as shown in the film, without any true paralysis. While there may be some doubt in diagnosing scrapie at its onset, the slow progress of the disease gives one ample time to reach a firm diagnosis as the clinical signs become well established.

"Turning now to the pathology of the disease, difficulty arises immediately. In a disease with such well defined clinical signs as scrapie, especially when disorder of function of the central nervous system is well established, one might be excused for expecting to find lesions, perhaps of a chronic nature, to account for the clinical signs. It is not so, however, because using customary histological methods Brownlee (1940) after an extensive study of most of the organs from scrapie sheep, found that the only constant abnormality was the presence of vacuoles typically of large size in the nerve cells of the medulla and spinal cord. This confirmed the original observations of Besnoit and Morel (1898) and other writers on the Continent and in this country. Brownlee examined 24 typical cases of scrapie and 64 non-scrapie sheep. In the sections he examined he found vacuolated neurons in the medulla oblongata and spinal cord of all sheep affected with scrapie, whereas in non-scrapie sheep examined in similar fashion, he found no vacuolated cells in the medulla or spinal cord, but drew attention to the occurrence, in a few instances, of typical vacuoles in cells of the spinal ganglia. The significance and specificity of this pathological change was doubted by the majority of the neuro-pathologists I consulted at that time and consequently Holman & Pattison (1943) repeated Brownlee's work with the intention of locating the distribution of vacuolated cells in the medulla oblongata and of determining their significance as a diagnostic aid in scrapie. They examined 75 cases of scrapie and 98 non-scrapie animals. While vacuoles were found in all scrapie-affected animals they also found vacuoles in 5 non-scrapie animals one of which was apparently healthy. This led them to conclude that the finding of vacuolated cells cannot be accepted as pathognomonic of the disease, but clinical symptoms suggestive of scrapie, followed by microscopic discovery of vacuolated nerve cells in the medulla oblongata, probably constitute sufficient evidence on which to base a positive diagnosis. Table I of Mr. Palmer's paper extends the work of Holman and Pattison to the examination of a bigger number of sections from each sheep and it is comforting to note that

3,492 vacuolated neurons were found in 190 sections from scrapie sheep whereas only 17 vacuolated neurons were found in 578 sections from non-scrapie sheep. This marathon task in histological examination to assess the significance of vacuolation of neurons in relation to scrapie continues, and Zlotnik and Rennie (1957[1]) have created a record by examining 180 serial sections from the medulla oblongata of each of 57 sheep of various breeds, a total of 10,260 sections. All these animals were apparently healthy at the time of slaughter and this comprehensive search showed that vacuoles were present in the neurons of 73.7 per cent. of the brains examined. The number of vacuoles found varied considerably from brain to brain, sometimes only one being found in the whole series from one brain after a long search while in a few brains the vacuoles were numerous, as many as 7 being seen in a microscopic field. At the moment Zlotnik's published evidence is confined to the examination of apparently normal animals. I very much hope that he can extend the same thorough search to a similar number of animals affected with scrapie in order to assess the comparative incidence of vacuoles in apparently normal and diseased animals. Clearly, Brownlee, Holman and Pattison, and now Palmer have all produced evidence that the incidence of vacuolated neurons in sheep affected with scrapie far exceeds that of sheep apparently free from scrapie when similar methods are adopted in examining the two groups, and since this knowledge is being extensively used, both in this and other countries, as an aid to the diagnosis of scrapie it is important that Zlotnik be given every encouragement to extend his work to the examination of a series of animals affected with scrapie with the same thoroughness that he has given to the examination of non-scrapie sheep. Since we succeeded in transmitting scrapie to goats, Pattison (1957) in a preliminary note records the finding of 2,279 vacuolated neurons in 94 sections from 16 scrapie-affected goats, and only 8 vacuoles in 592 sections of 16 clinically healthy goats. Here again in another species the rise in incidence of vacuolated neurons in affected versus non-affected animals is striking. Mr. Palmer's Table III also shows a high incidence of vacuolated neurons in affected goats. Here I would like to ask Mr. Palmer if he has worked out a basis on which he would be prepared to diagnose scrapie by histological examination in the absence of a clinical history?

"Just before this meeting Mr. Palmer drew my attention to a letter by Zlotnik in *Nature* this week, August 24th (1957[2]) which has arrived at a most opportune moment. It describes the comparative incidence of vacuolated neurons in 10 scrapie sheep versus 10 apparently healthy sheep. Fifty-four sections were examined from each animal and while 25,989 vacuolated neurons were found in the scrapie-affected animals only 151 vacuolated neurons were found in apparently healthy sheep. In the face of this evidence can anyone doubt that there is a rise in the incidence of vacuoles in sheep affected with scrapie? Its pathological importance has yet to be determined.

"Here one is tempted to say that the field of scrapie research is populated by two kinds of sceptics, those who do little or no work on the disease and who remain sceptical about existing evidence, and those who undertake work to prove that the existing information is wrong but from the results they obtain become converts to believing in the existing evidence.

"The intravacuolar material seems to have been found by Mr. Palmer more frequently than has been the experience of others, possibly his technique is better, and the presence of this material in vacuoles in efferent nerve fibres as shown in Fig. 2 is, to me, new and exciting. New to me also are the bodies in the cytoplasm of apparently non-vacuolated neurons from affected sheep, as shown in Fig. 6, and the extracellular round bodies as shown in Fig. 9. While all these observations are interesting their significance in the pathology of scrapie is difficult to assess, and if it is not an unfair question I should like to ask Mr. Palmer if as an aid to diagnosis he places more significance on the finding of vacuoles in the neurons of the medulla than to any of the other changes he has described?

"One last word on vacuoles. Mr. Palmer found that in non-scrapie sheep the vacuoles present were mainly confined to the dorsal nucleus of the vagus. In Zlotnik's series of apparently healthy sheep he states that vacuoles were mostly in the dorsal motor vagus nucleus. Thus there is a large measure of agreement that most of the vacuolated neurons in sheep not affected with scrapie, are in the dorsal nucleus of the vagus. This raises the interesting possibility that the specificity of the histological aid to diagnosis might be increased by ignoring vacuoles in the dorsal nucleus of the vagus. I present this thought jointly to Palmer and Zlotnik for further exploration.

"Turning now to the question of myopathy and the relationship of this condition to scrapie as described by Bosanquet, Daniel & Parry (1956) and Parry (1957). Mr. Palmer concludes, on the evidence of his investigations, that while myopathy can occur in sheep and goats it is unlikely to be responsible for the complicated nervous manifestations of scrapie. Dr. Daniel and Mr. Parry kindly visited

TABLE I

LOUPING-ILL VACCINE 1935

Batch I	Batch II	Batch III
25,000 doses	18,000 doses	5,000 doses
	Prepared from 114 sheep; 8 were yearlings born in 1934 from ewes which began to develop scrapie 15 months later in 1936. Some surviving lambs, fellows to the 8 used for vaccine in 1935, developed scrapie in 1936/7.	
No scrapie	Scrapie developed in 7 per cent. of inoculated animals	No scrapie

Compton and demonstrated the exhaustive nature of the examination that has to be made when searching for lesions of myopathy. It involves the complete dissection of the musculature. Mr. C. D. Bracewell of our staff examined 8 natural cases of scrapie by this method accompanied by histological examination without finding any of the myopathic lesions of Bosanquet, Daniel & Parry. Further, Mr. Pattison at Compton has kept a careful watch on both sheep and goats affected with scrapie with negative results. Dr. Stamp, of Moredun Institute, in a private communication, told me he had dealt with 14 natural and 12 experimental cases of scrapie in which every muscle was examined in detail, including preparation of sections from representative samples. These examinations had disclosed nothing resembling the lesions as depicted by Bosanquet, Daniel & Parry. While it is clear from their work that myopathy can be found both in sheep affected with scrapie and sheep not affected with scrapie, it is equally clear from the work of others that many sheep affected with scrapie do not have myopathy. In view of this evidence it is difficult to accept myopathy either as the cause or the essential pathology of the disease. A possible explanation for this discordant result may be that in addition to scrapie myopathy was particularly prevalent in the sample of sheep examined by Parry.

"What then is the cause of scrapie? I believe it to be caused by a transmissible agent the nature of which has still to be determined. This agent has been passed in series from sheep to sheep by cell free filtrates of tissues from the central nervous system, Wilson, Anderson & Smith (1950). At Compton it has been transmitted from sheep to goats and back to sheep again producing the typical clinical signs in the sheep and it has now been passed in series to the third generation in goats. The agent could be defined as a filter passing virus were it not for the fact that it can withstand temperatures that make it difficult to believe it is a living agent. Nevertheless, it appears to increase in quantity or to multiply in inoculated animals. The incubation period is long, being 4 to 15 or 24 months after inoculation, and it is difficult to explain why only about 50 per cent. of inoculated sheep develop the disease.

"It has previously been reported that of three batches of louping-ill vaccine issued in 1935 one was responsible for transmitting scrapie to sheep on farms where the disease had not been known before (see Table I).

"This led to a transmission experiment as shown in Table II with a result as depicted in Table III. For the purpose of this experiment South Scotland Cheviot stock on a farm in Eskdalemuir that was being taken over by the Forestry Commission for the planting of trees was purchased. This stock was bound to the ground and had a history of complete freedom from scrapie. The result provides evidence that scrapie is a transmissible disease and that it can spread by cohabitation from affected to healthy sheep.

"Following this experiment other activities prevented me from continuing the investigation of scrapie until 1953, but in the intervening years Dr. D. R. Wilson, of Moredun Institute, built up a mass of evidence some of which has been published, Wilson, Anderson & Smith (1950), which confirms that scrapie is a transmissible disease, that the transmissible agent passes filters that withhold bacteria, that it can be passed in series from sheep to sheep and that it can withstand temperatures and inactivating agents normally expected to kill living organisms. In future experiments both in sheep and goats due attention will have to be given to the spread of the disease by contact.

"In this country, while the disease was a nuisance, it was not a major economic problem until 1952 when it developed in British sheep exported to Canada, New Zealand and

TABLE II

PLAN OF SCRAPIE TRANSMISSION EXPERIMENT 30/8/38 TO 31/10/42 IN SOUTH SCOTLAND CHEVIOT SHEEP

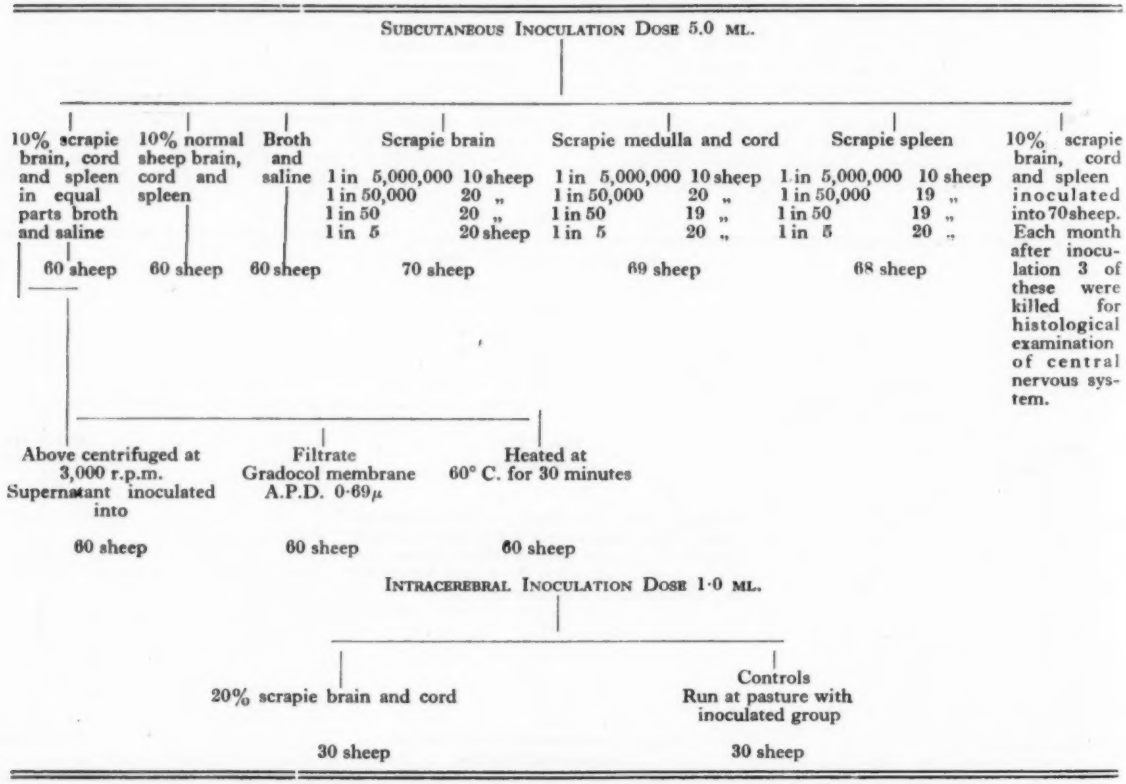
Subcutaneous Inoculation Dose 5.0 ml.
10% scrapie brain, cord and spleen in equal parts broth and saline
60 sheep
10% normal sheep brain, cord and spleen
60 sheep
Broth and saline
60 sheep
Scrapie brain
1 in 5,000,000 10 sheep
1 in 50,000 20 „
1 in 50 20 „
1 in 5 20 sheep
Scrapie medulla and cord
1 in 5,000,000 10 sheep
1 in 50,000 20 „
1 in 50 19 „
1 in 5 20 „
Scrapie spleen
1 in 5,000,000 10 sheep
1 in 50,000 19 „
1 in 50 19 „
1 in 5 20 „
70 sheep
69 sheep
68 sheep
10% scrapie brain, cord and spleen inoculated into 70 sheep. Each month after inoculation 3 of these were killed for histological examination of central nervous system.
Above centrifuged at 3,000 r.p.m. Supernatant inoculated into
60 sheep
Filtrate Gradocol membrane A.P.D. 0·69μ
60 sheep
Heated at 60° C. for 30 minutes
60 sheep
Intracerebral Inoculation Dose 1·0 ml.
20% scrapie brain and cord
30 sheep
Controls Run at pasture with inoculated group
30 sheep

TABLE III
SUMMARY OF RESULT OF SCRAPIE TRANSMISSION EXPERIMENT 1938 TO 1942

Route of inoculation	Inoculum	Number of sheep	Incidence of scrapie				First case in time after inoculation
			Within 2 years of inoculation		Up to 4 years 2 months after inoculation		
			Affected sheep	Per cent.	Affected sheep	Per cent.	
Subcutaneous	Saline and broth, equal parts. Suspending fluid for all tissues	60	0		5	8	30 months
	10 per cent. normal sheep brain, cord and spleen	60	0		3	5	29 „
	10 per cent. Scrapie brain, cord and spleen	60	8	13	22	37	15 „
	Supernatant fluid from Centrifuged scrapie brain, cord and spleen, 3,000 r.p.m.	60	11	18	25	42	16 „
	Gradocol membrane filtrate of above supernatant fluid. A.P.D. 0·69/μ ...	60	4	7	19	32	19 „
	Scrapie brain, cord and spleen. Heated at 60° C. for 30 minutes	60	5	8	17	28	18 „
	Scrapie brain excluding medulla :						
	1/5,000,000	10	0		2	20	38 „
	1/50,000	20	1	5	8	40	20 „
	1/50	20	1	5	5	25	19 „
	1/5	20	3	15	9	45	17 „
	Scrapie medulla and cord :						
	1/5,000,000	10	0		0		———
	1/50,000	20	0		8	40	29 „
	1/50	19	3	16	6	32	17 „
	1/5	20	7	35	8	40	19 „
	Scrapie spleen :						
	1/5,000,000	10	0		2	20	30 „
	1/50,000	19	0		4	21	28 „
	1/50	19	1	5	6	32	24 „
	1/5	20	1	5	5	25	24 „
Intracerebral	20 per cent. Scrapie brain and cord ...	30	13	43	20	67	7 „
Not inoculated	Controls	30	0		1	3	42 „
Subcutaneous	10 per cent. Scrapie brain, cord and spleen	70					

3 sheep killed each month after inoculation for histological examination of medulla. Vacuoles were not observed in the nerve cells until clinical signs were manifest at 21 months.

Australia, which resulted in these countries and the United States of America placing a ban on the importation of sheep from Britain. In U.S.A. eradication by means of a slaughter policy is in progress and much valuable information on the epidemiology and spread of the disease is being obtained. Under the aegis of a technical committee of the Agricultural Research Council a considerable programme of investigation is in progress at Moredun Institute, Edinburgh, the Agricultural Research Council Field Station, Compton, and the School of Veterinary Medicine, Cambridge."

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After other delegates had contributed to the discussion Dr. Gordon said he wished to refer to a point which arose from Professor Amoroso's remarks about the possibility of vacuoles being artifacts. A renowned neuropathologist had said that he could reproduce that kind of thing as an artifact, but before his death he wrote to Dr. Gordon and said that the vacuoles were not artifacts. He further indicated that they seemed to be associated with sheep affected with scrapie. In his examinations he had not found vacuoles in the normal sheep.

Dr. Gordon said that when he started work on the subject of scrapie he chose a Welsh mountain breed, as it was

an ecomonic sheep to buy. He purchased 650 of them with a view to checking whether the Welsh mountain breed could be infected with the disease. He inoculated 12 Welsh mountain and 6 South Scotland Cheviot sheep. None of the Welsh mountain sheep developed the disease, whereas 4 of the 6 South Scotland Cheviots did develop it. He then used 120 Welsh mountain sheep. There were 10 different groups inoculated with 10 different sorts of material. In one group of 30 which were inoculated with scrapie-infected material, one solitary animal developed scrapie. He had made a film of that animal, indicating symptoms similar to those which Mr. Palmer had shown in his film. Material was taken from that sheep and put into Cheviot and Welsh mountain sheep, there being 30 in each group. Of the Cheviot sheep group, half developed scrapie, and of the Welsh mountain group, none developed the disease until several months after the Cheviots, and then only 4 developed it. His impression was that it was not easy to transmit the disease to the Welsh mountain breed, and he had never heard of scrapie developing naturally in that breed. To Mr. Milton, of Brecon, he said, "I think you can go back to Wales and tell the farmers there not to worry."

Mr. Milton, replying to Dr. Gordon's concluding remarks, said that he wished to make it clear that in his part of Wales he was much more concerned with the Cheviot than the Welsh mountain breed of sheep. At least 50 per cent. of the sheep farmers in his area went to Scotland to buy Cheviot lambs, and at least 50 per cent. of the flocks were Cheviot.

The General Discussion

Dr. P. J. G. Plummer, from the Animal Diseases Research Institute, Hull, Canada, thanked Mr. Palmer for his valuable contribution to the literature. He was of the opinion that myopathy was not associated with scrapie. He had not observed the condition in any incident, 40 to 50 sheep examined. For several years he had regarded the presence of certain eosinophilic cytoplasmic inclusion bodies as pathogonomonic for the disease but recently had been shown at the Moredun Institute, identical bodies in the brains of sheep not affected with scrapie. From this he has to change his view as to their significance.

Professor Dr. H. Behrens (Hanover): "At first I should like to express my great thanks that I can take part in your Congress. I should like to mention that 50 and more years ago scrapie was a very widely distributed disease in Germany. The disease mostly appeared in Merino flocks kept in central and eastern parts of Germany. A great number of individual and even entire flocks were slaughtered because of this disease which was thought to be a hereditary one. Since about 12 years ago scrapie has disappeared from Germany, not only in flocks which are kept in the western zone but as far as the situation of the eastern zone is known to me, there too. I am sorry I can't tell you why, and how, scrapie disappeared from my country."

The Reply

Mr. Palmer, replying to the discussion, said that it would be dangerous to attempt a diagnosis of scrapie in the absence of history. As he had shown, in some cases of scrapie there were few vacuolated neurons. On the other hand, if he were presented with 10 sections of a medulla, with an average of 20 vacuolated neurons per section, he would suspect that the animal was affected.

Dealing with a point raised by Professor Amoroso, he said that he agreed that a number of the animals on which he had experimented were young; he was doing some more work using older animals as controls. He had undoubtedly found vacuolation in his control animals, but in most cases the vacuolation occurred in nerve cells of the dorsal motor nucleus of the vagus.

With regard to the intra-vacuolar material he had found consistently in a large proportion of vacuolated neurons. He did not know what was the nature of the extra-vacuolar material, and he would be grateful to know if any of his listeners had any ideas on the subject.

With regard to the fixation of the tissue for this work, he had tried a dozen methods. The morphology of the vacuoles was the same under all these separate conditions.

The Natural History of Parasitic Bronchitis with Notes on Prophylaxis and Treatment

BY

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DURING the past five years we have carried out research into parasitic bronchitis dealing with its epidemiology, pathology, clinical features and immunology. This paper covers in a general way all of these aspects which have been, or are in process of being, reported in greater detail in the more specialised scientific journals. Our investigations have largely been confined to the disease *per se* and one major aspect of the natural history of *Dictyocaulus viviparus* as distinct from that of parasitic bronchitis has been omitted, *viz.*, the bionomics and ecology of the larval forms in the few months preceding the season in which the disease occurs.

The pattern of field and experimental work was designed mainly to cover the following problems:—

(1) How does the disease persist from year to year on a farm?

(2) What is the correlation between the clinical signs and pathological features of the disease and how many syndromes are encompassed?

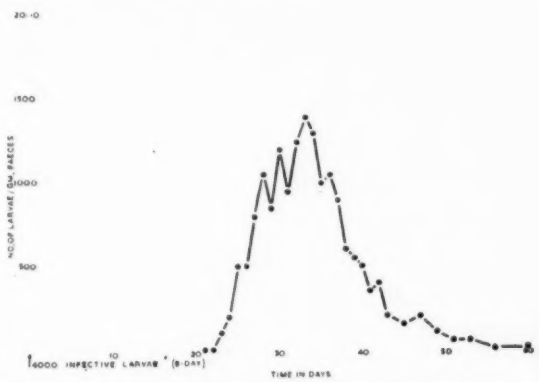
(3) What are the criteria necessary for the diagnosis of parasitic bronchitis?

(4) What is the pattern of immunity to the disease and how might this be accomplished artificially?

We believe that we have found the answers to all these questions and in this paper are set out stage by stage the development of the disease and the natural and artificial immunity to it. The material studied consisted of many field outbreaks and several hundred experimental calves. For clarity the experimental disease is used as the main basis for description, and reference is made to the field syndrome where appropriate.

Experimental Parasitology

The method of obtaining infective larvae for producing the disease is of the utmost importance since some methods (*e.g.*, the use of the Baermann apparatus) give results so irregular as to render it impossible to get reproducible results from experiment to experiment and they also give rise to a wide range of infectivity. We have used the very simple technique of placing faeces containing first-stage larvae in jars in a moist atmosphere at room temperature for 7 to 10 days. After this time most of the third-stage larvae have migrated to the surface of the faeces or onto the side of the jars. These are washed off with tap water and the resulting suspension gives larvae of a high percentage motility and infectivity. Suitably diluted amounts are administered to experimental calves by drenching. A typical result of administering 4,000 infective larvae is shown in Graph 1.



GRAPH 1.—Faecal larval output in a calf infected with 4,000 larvae.

The administration of 4,000 larvae generally results in the establishment of approximately 1,000 adult worms in the bronchi, and the faecal larval counts in such an animal range from 200 to 1,500 per gm. Using the techniques described above the ratio of 4 or 5 : 1 (larvae administered: worms recovered from bronchi) is approximately correct for dosage ranges from 500 to 5,000 larvae. The scatter of worm counts to be expected from 10 calves (the control group in one experiment) given 4,000 larvae each in a single dose is shown in Table I; the numbers obtained from calves given 2,000 and 500 larvae each are shown in Tables II and III respectively. Table IV shows the number of adult worms recovered from 10 calves given 200 larvae every second day for 20 days (2,000 total) and Table V the results when the calves were given 50 every second day (500 total) for the same period.

TABLE I

THE NUMBERS OF WORMS RECOVERED AT AUTOPSY FROM 10 CALVES EACH INFECTED WITH 4,000 THIRD STAGE LARVAE AS A SINGLE DOSE

Calf No.	1	2	3	4	5
No. of worms	825	840	1,452	1,788	992
Calf No.	6	7	8	9	10
No. of worms	180	1,081	1,100	950	1,220

TABLE II

THE NUMBERS OF WORMS RECOVERED FROM NINE CALVES EACH INFECTED WITH 2,000 LARVAE AS A SINGLE DOSE

Calf No.	1	2	3	4	5
No. of worms	120	450	590	550	380
Calf No.		6	7	8	9
No. of worms		226	137	330	180

TABLE III

THE NUMBERS OF WORMS RECOVERED FROM 10 CALVES GIVEN A SINGLE DOSE OF 500 LARVAE

Calf No.	1	2	3	4	5
No. of worms	96	221	105	88	94
Calf No.	6	7	8	9	10
No. of worms	53	80	115	70	50

TABLE IV

THE NUMBERS OF WORMS RECOVERED FROM 10 CALVES GIVEN 10 DOSES OF 200 LARVAE ON ALTERNATE DAYS

Calf No.	1	2	3	4	5
No. of worms	480	203	240	277	195
Calf No.	6	7	8	9	10
No. of worms	212	164	333	224	312

TABLE V

THE NUMBERS OF WORMS RECOVERED FROM 10 CALVES GIVEN 10 DOSES OF 50 LARVAE ON ALTERNATE DAYS

Calf No.	1	2	3	4	5
No. of worms	69	90	56	83	111
Calf No.	6	7	8	9	10
No. of worms	63	65	80	56	73

Numbers of adult worms are easily estimated by manual removal from the bronchi with forceps: immature forms are counted by washing out bronchial mucus with saline and subsequently sedimenting and by mincing lungs and subjecting the homogenate to Baermannising over warm saline.

Pathogenesis

The pathogenesis of the disease has been elucidated by infecting calves with a range of doses of larvae and killing them at selected intervals. Most work has been done using doses of 5,000 and 50,000 larvae and killing pairs of calves every second day up to 20 days and 5- to 10-day intervals thereafter up to 120 days after infection. These doses were selected because 5,000 larvae produce the syndrome of severe but non-fatal husk, as seen in the field, and 50,000 larvae produce acute (fog-fever-like) fatal illness before the 18th day after infection, *i.e.*, in the prepatent period.

Lesions produced by 5,000 and 50,000 larvae are qualitatively similar differing only in degree until the immediate *pre-mortem* stage is reached in the 50,000 infections. They will therefore be described together.

The development of the disease may be conveniently divided for pathological and clinical purposes into four phases.

(1) *Penetration of Bowel and Migration to Mesenteric Nodes*

The infective larvae penetrate the small intestine and upper colic region *via* the crypts causing a subclinical catarrhal enteritis (Fig. 1). Their passage through the lamina propria of the bowel (in non-immune animals) does not appear to give rise to a marked reaction. From the third day onwards they are present in the mesenteric nodes and a marked giant cell and macrophage reaction to them occurs (Fig. 2). It is believed that this is the site of the primary immune stimulus. In immunised animals eosinophil reaction is added and many larvae die, subsequently becoming calcified.

(2) *The Alveolar-Bronchial Phase*

Lesions due to migrating larvae can be demonstrated in the lungs from five days after infection. In the alveoli they produce a moderate degree of macrophage and eosinophil reaction and are attacked by multinucleated giant cells (Figs. 3 and 4). The degree of consolidation and hence the magnitude of clinical signs, depends on the number of larvae present at one time, *e.g.*, in 50,000 larvae infections collapsed areas are found in all lung lobes and there occurs a diffuse interstitial eosinophil infiltration.

As the larvae ascend the bronchioles eosinophil leucocytes play a dominant part in the production of lesions. Marked peribronchial cuffing by these cells occurs (Fig. 5) and individual migration of eosinophils through the epithelium gives rise to a cribriform vacuolation and ultimately tattering and ulceration of the tubular lining (Fig. 6). The smaller air passages become plugged with eosinophil exudate and collapse of the related alveoli supervenes. Simultaneously epithelialisation of non-collapsed alveoli takes place and all of these changes together may produce a considerable degree of respiratory embarrassment. It is to be noted that at this time the nematodes are mainly in the medium and larger bronchi and in the trachea and that they are too small in size to cause clinical signs by obstruction of the air passages; the pathological effects are caused by the pulmonary reaction to the parasites.

No calf given 50,000 larvae survived beyond the 16- to 18-day period and the lesions found in these were qualitatively different from those found in calves with lighter infestations. The principal lesions for the former cases are those described above plus emphysema and alveolar and lobular oedema with hyaline membrane formation.

This last lesion is of great importance in husk and explains many formerly puzzling clinical signs. The presence of diffuse eosinophilia, lobular consolidation and collapse, alveolar epithelialisation and acute bronchial damage produces a stage of anoxia. This is reflected in impaired cardiac function which in turn gives rise to pulmonary oedema. When alveoli containing oedema fluid are exposed to considerable hyperventilation it may be that a large proportion of water is evaporated from the oedema fluid and a film

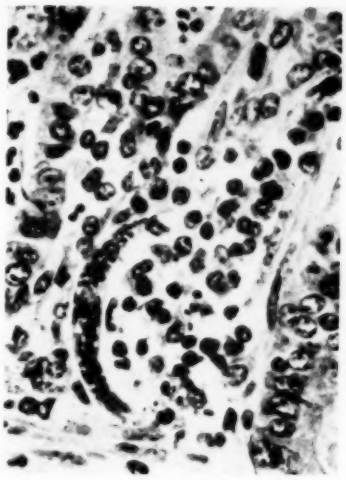


FIG. 1.—Third stage larvae penetrating the bowel wall.

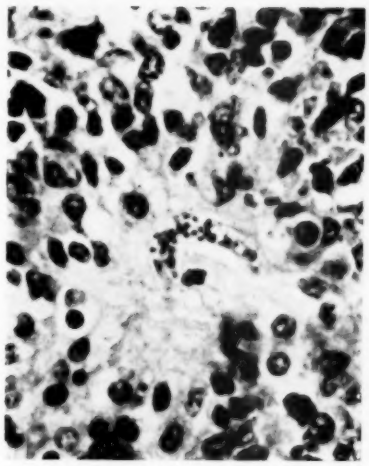


FIG. 2.—Larvae in necrotic tract in mesenteric node with surrounding inflammatory reaction.

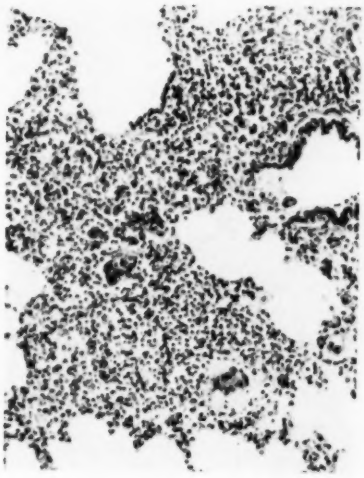


FIG. 3.—Lung seven days after infection showing consolidation and giant cell reaction to migrating larvae.

FIG. 4.—Lung. Larvae in alveolus surrounded by intense eosinophil reaction. Nine days after infection.

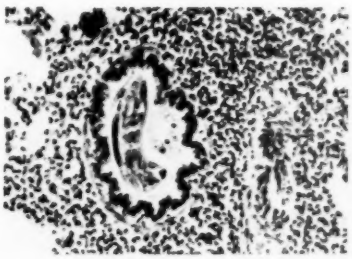


FIG. 5.—Larvae in terminal bronchiole, the latter being surrounded by a cuff of eosinophil leucocytes. Nine days after infection.

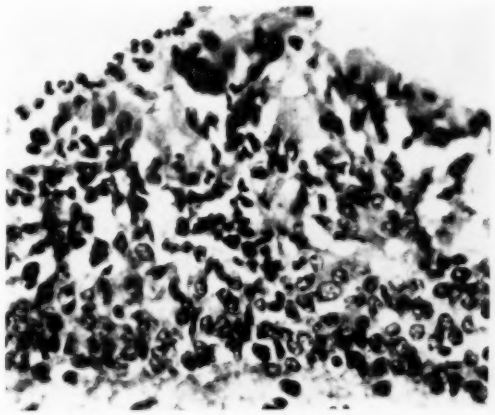


FIG. 6.—Bronchial epithelium being heavily vacuolated by intense eosinophilic infiltration

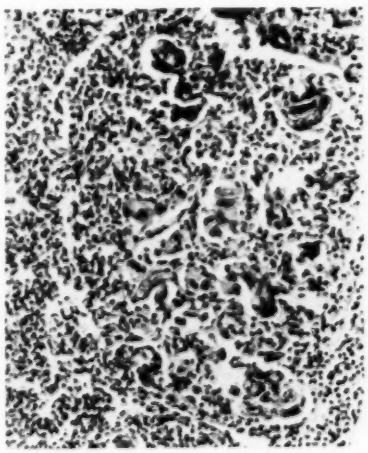


FIG. 7.—Alveolar consolidation in lung caused by foreign body giant cell reaction to first stage larvae.

FIG. 8.—Egg containing a larva surrounded by a foreign body type giant cell.

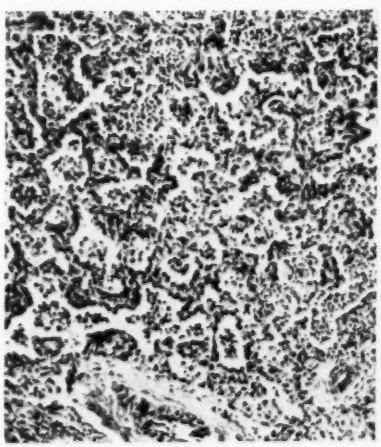


FIG. 9.—Diffuse lobular epithelialisation of alveoli.

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of coagulated plasma protein is laid down as a lining around the alveolar walls. This increases the stage of anoxia and so a form of anoxic "vicious circle" is set up.

The onset of pulmonary oedema and hyaline membrane formation can occur very rapidly and accounts for many of the acute deaths of the so-called "fog fever" type to which reference is made below.

(3) *The Patent Phase*

Lungworms which have become adult in the bronchi reach maturity and begin to lay eggs about 24 days after infection. The typical clinical signs of the "typical" husk case at this stage when larvae can be demonstrated in the faeces have multiple causes and are not due merely to bronchial blockage by worms. These causes are: (i) the obvious obstructive effect of the worms, although this is not marked in a proportion of cases; (ii) the damage to the bronchial epithelium caused by the migration through it of large numbers of eosinophil leucocytes; (iii) the aspiration back into alveoli of large numbers of eggs and first-stage larvae. This gives rise to a "foreign body" reaction (Fig. 7) in which the lobules are consolidated by the formation around larvae and eggs (Fig. 8) of large multinucleated giant cells and macrophages. This constitutes the extensive pneumonia seen at autopsy in typical husk cases and it is not due to secondary bacterial reaction as is commonly supposed. The associated greenish pus found in the bronchi is not suppurative in origin but is composed of many degenerating eosinophil leucocytes; (iv) the interstitial septa of the lungs become highly oedematous and their lymphatics grossly distended. This produces the well-known "marbling" effect seen at *post mortem*; (v) interstitial emphysema may become very widespread. A study of serial sections has led us to postulate its pathogenesis as follows. Under the action of tachypnoea and dyspnoea the terminal bronchioles become distended. Many of these small air passages run close to septa at the edges of lobules and turn back sharply into lobules as recurrent or circumflex bronchioles; at this point their wall is very weak and in the animal in respiratory distress, rupture takes place at this point, air thus gaining entrance to the septal tissues and lymphatics. Since this air is tidal, large interstitial bullae may be formed and air may pass to the mediastinal lymph nodes and loose connective tissue of the mediastinum and thence to the thoracic inlet and out into the subcutaneous tissues where it may be palpated with the well-known "crackling" effect; (vi) from the 35th day onwards alveolar epithelialisation may become fairly widespread. The alveoli are lined by cuboidal epithelium which inhibits proper transfer of gases between blood and air spaces (Fig. 9).

(4) *The Late Patent and Post-patent Phase*

The main lesion is the alveolar epithelialisation mentioned above. At this stage (45 plus days after infection) the numbers of adult worms in the bronchi gradually diminish and finally they disappear; animals may, however, continue to show clinical signs when no larvae can be demonstrated in the faeces and no worms can be found in the bronchi. At autopsy considerable degrees of consolidation are found, the lobes having an unusual crepitance and being rubbery to feel. This is due to alveolar epithelialisation causing thickening of the alveolar walls while the alveoli still contain air (Fig. 9). The precise cause of the lesion is not yet known but it is suspected that it may be due to the presence in the lungs of dead adult lungworm tissue since the lesion is often most marked around such deposits.

The main residual lesions seen later than 70 days after infection are peribronchial fibrosis and intrabronchial granulomatous polyps. In some cases bronchiectasis develops in the dependent anterior lobes and may give rise to a chronic pining animal.

Clinical Correlation

The Alveolar-Bronchial Phase

From the fifth to the ninth days after infection with mild and heavy infections the normal calf which has been breathing at the rate of 15 to 25 times per minute and has been showing no signs of coughing begins to breathe a little faster and coughs occasionally. The short vesicular sound heard on auscultation in the normal animal becomes prolonged and harsher. By the end of the second week there is a marked difference between the different levels of infection studied. Those which have received 50,000 larvae are seriously ill with respiratory rates ranging from 35 to 60 per minute. Apart from coughing and some slight elevation in respiratory rate the calves receiving the lower dosage level show relatively little abnormality.

During the third week following infection the heavily infected calves invariably die, gasping for breath with short, shallow respirations. Auscultation reveals harsh bronchial respirations with emphysematous crackling. These calves become anorexic a few days before death. During the last 24 hours of life a rapid weakening of the median pulse is noticeable, the respiratory rate lowers and an expiratory grunt develops. In some cases oedematous râles can be heard. This is the characteristic "fog fever" syndrome encountered in the field in both calves and cows.

The calves receiving 4,000 to 5,000 larvae become progressively worse during the third week. Respiratory rates approach 100 per minute and appetite and growth rate are diminished. Harsh bronchial breathing, an occasional rhonchus and possibly some emphysema are heard on ascultation.

The Patent Phase

This phase is reached during the fourth week following infection and the severity of clinical signs reach their peak during this phase. In a typical outbreak requiring the interference of the veterinary surgeon at least half the animals affected will be in this phase. Calves which received 4,000 to 5,000 larvae will develop a respiratory rate between 100 and 120 per minute, slightly faster than their cardiac rate. Coughing becomes more frequent and appetite and growth rate reach almost zero. Rhonchi and emphysematous crackling can be heard over the harsh bronchial breathing. Thoracic resonance

varies with the balance of emphysema and consolidation. An increase is not uncommon but it is usually difficult to establish a clear-cut decrease in resonance.

The condition of the individual calf often remains static for about a week, but towards the end of the fifth week and during the sixth week following infection a steady improvement begins. By the end of eight weeks calves are usually eating well and putting on weight, but coughing still persists and the respiratory rate is noticeably elevated. Indeed coughing and slightly harsher and faster respirations may continue for several months. The extreme form of this aftermath is represented by bronchiectasis which is responsible for the bad condition of many yearlings after their first season at grass. There is a considerable mortality among those animals during the spring months.

The above description of the patent phase has been based on those animals infected with 4,000 to 5,000 larvae. Calves receiving doses of 1,000, 2,000 larvae and repeated small doses of 100, 200 and 500 larvae have also been observed clinically in both the alveolar-bronchial phase and the patent phases. Following infection there was a similar gradual development of coughing, tachypnoea and bronchial inspirations but at no time did the respiratory rate become greater than 50 to 70 per minute and in many cases it was much lower. Appetite usually continued at a normal level and weight gains were not reduced. None the less, slight tachypnoea continued for several weeks and coughing for several months.

The above observations carried out on experimental animals offer an explanation for the great variation in the severity and type of clinical signs which we encountered in the field in different outbreaks and in different animals in any one outbreak. In any animal the severity of clinical signs will depend on the total number of larvae and the period of time over which they are ingested. In addition the different animals in any one group will be at different stages in the development of the disease and this will add to the variation in clinical signs. Yet another factor which may increase the severity of the disease is the presence of another type of pneumonia before the animal is exposed to husk.

Epidemiology

Before we had evolved an efficient method of vaccination against parasitic bronchitis we attempted to elaborate a method of management which would prevent or modify the severity of the disease and to this end a study of some of the epidemiological factors involved was undertaken. Two main problems were investigated. (1) How long can larvae persist on pasture? (2) What is the status of the carrier animal?

On the question of larval survival two types of experiment were carried out. First, paddocks of grass were grazed by calves which had been artificially infected and were excreting large numbers of larvae in their faeces. These paddocks were fenced off and approximately one year later young susceptible calves turned onto this pasture contracted parasitic bronchitis. Secondly, small pots of grass were contaminated with faeces containing lungworm larvae and left out through the winter on the roof of a building. At three-monthly intervals the contents of pots were homogenised and administered to susceptible calves reared in isolation. In this way it was shown that pots of nine months of age contained viable infective larvae. These two experiments, the first of which was repeated successfully in a second year, demonstrated that in the climatic conditions obtaining in the west of Scotland, lungworm larvae can survive the winter on pasture and such contaminated pastures must be recognised as potentially dangerous in the maintenance of the disease on a farm.

Figures of the incidence of carrier animals were obtained by studying 1,500 pairs of lungs from two knackeries during the months of January to May when husk is not usually found as a clinical disease. The results showed that during this time 30 per cent. of yearling animals and 4 per cent. of adults harboured small numbers of lungworms in their bronchi. Hence it was conclusively shown that the carrier yearling is a major factor in the propagation of the disease. In addition, by visiting the farms from which these carriers came, it was found that many had been kept in conditions which probably precluded continued reinfection indicating an extended life cycle period in these cases.

Diagnosis

Clinical

The appearance of a group of young calves at grass for the first time coughing repeatedly, breathing rapidly and thriving badly in the autumn is almost pathognomonic of "husk," but it is important to remember that the individual animal from such a group will show a syndrome of pneumonia which simulates completely the signs expected of any proliferative type of pneumonia. In many cases cuffing pneumonia has been found along with husk at autopsy. If absolute confirmation of the presence of husk is required then parasitological and/or histopathological techniques are required.

There are two sets of circumstances in which the diagnosis of husk leads to confusion. In outbreaks of cuffing pneumonia in indoor calves many of the features are found to be similar to husk. Some of the outbreaks appeared to have started among indoor calves soon after the return from grazing of animals affected with husk and in two such instances we have found evidence of lungworms present in the calves which had never been outside. On four occasions hay suspected by the farmer to contain larvae was fed to experimental calves without producing disease.

The other important source of confusion concerns the syndrome commonly known as "fog fever" as it occurs in adult animals. Clinically, this is no different from severe forms of husk which we have encountered and is characterised by acute dyspnoea and tachypnoea with or without rhonchi, emphysematous crackling and oedematous râles. The animals normally die from anoxia and cardiac failure with or without the presence of pulmonary oedema at autopsy. With one exception the histopathological examination of autopsy material from such cases examined by us or sent by veterinary surgeons from

many parts of Britain has revealed the typical picture of husk.

Parasitological

The presence of lungworm infestation can be confirmed in the living animal by the demonstration of larvae in the faeces and at autopsy by the finding of nematodes in the lungs.

(1) For the demonstration of larvae in the faeces we recommend the McMaster technique. If both sides of the chamber are counted, quantities of over 25 larvae per g. can be detected. More refined methods (Baermann: zinc sulphate flotation) are available but are of no help in assessing clinical cases since it is doubtful if counts of less than 50 per g. are of much help to the clinician since carriers and "normal" animals in endemic areas may show small counts; respiratory symptoms in such cases may or may not be due to husk. Counts of 100 to several thousand larvae per g. are found in typical cases during the patent period but marked differences in numbers of larvae per g. in any individual case may be found from day to day. Negative counts are to be disregarded in assessing final clinical diagnosis since animals may become severely ill and may die, as has been shown above, in the pre- and post-patent phases of the disease when larvae are absent from the faeces.

Such cases may be diagnosed in the pre-patent phase by examining simple smears of bronchial mucus microscopically for the presence of immature lungworms. A laboratory technique for this purpose consists in washing out all the bronchi with saline and concentrating the sediment for microscopical examination and simultaneously mincing the lungs and subjecting them to the Baermann technique over warm saline.

Pathological

Parasitic bronchitis may be easily diagnosed histologically at all phases of the disease. At least six small blocks should be cut from obviously consolidated areas, fixed in approximately 10 per cent. formalin and dispatched to a laboratory which handles this type of material.

Treatment

The most important measure in treating a group of affected animals is to remove them from the source of infection and take them inside or into a Dutch barn. The cost of feeding those animals indoors represents one of the greatest sources of financial loss from this disease. Nevertheless, the risk of much heavier losses resulting from leaving the animals on the affected pasture cannot be undertaken lightly. On the other hand it should be made clear to the owner that the affected animals may still become worse indoors, and that some which are not showing signs may begin to do so. This is because of the delay of two to four weeks already described between ingestion of larvae and the peak of severity of clinical signs. Once inside it is advisable to separate the severely affected cases from the milder ones so that the food and water intake of the severe cases may be individually supervised. When an animal is anorexic it is most important to see that it receives at least half a gallon of water per live hundredweight daily, by drenching if necessary.

Over 20 substances have been tested for their activity against the adult worms in the bronchi without success. Antibiotics are of value in severe cases to limit the spread of bacterial complications.

In the severe cases showing the "fog fever" syndrome the most important part of the treatment is oxygenation. Oxygen may be led directly into the trachea from its cylinder *via* pressure tubing and a needle. It may be administered economically for several days if necessary. Within a few minutes of oxygen being administered there is a marked reduction in the respiratory rate often accompanied by the disappearance of any expiratory grunt. Where circulatory collapse has set in digitalis may be used along with oxygen to improve cardiac output.

The prognosis of a case should never be considered severe enough to prevent the animal's receiving oxygen and digitalis. Some remarkable recoveries can be obtained by the persistent application of this type of therapy.

Immunology

It has frequently been noted that a strong acquired immunity is associated with *D. viviparus* infection in the field. Our work has covered a study of the naturally acquired immunity, and an investigation into methods for the production of an immunity artificially.

We have been able to confirm the field observations on acquired immunity both by challenge of recovered field cases of the disease and by attempted reinfections of experimental animals. In the course of these and our other immunological experiments the level of complement-fixing antibodies in the serum of the experimental animals was determined by a quantitative complement fixation test of the 50 per cent. haemolysis unit type.

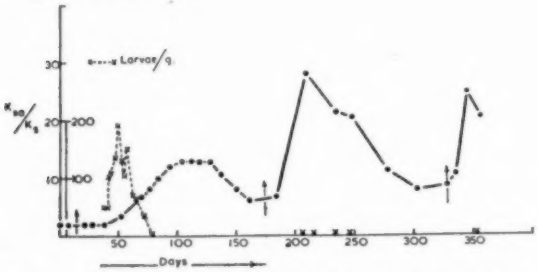
(a) *Reinfection of field cases*

Ten animals which had been fairly severe natural clinical cases were brought indoors and an attempt to reinfect them was made by administering up to 100,000 larvae (this is 20 times the dose required to produce severe husk). In some of the animals respiratory symptoms occurred about one week after challenge but these were transient and in no case did the disease become patent. In all cases there was a sharp rise in the serum level of complement-fixing antibodies characteristic of a secondary response (*vide infra*).

(b) *Experimental infection and reinfection*

Ten calves were infected with 2,500 larvae each, followed six months later by 4,500 larvae each and again six months later with 13,000 larvae each. All animals were killed 32 days after the last infection. The mean-levels of C.F. antibodies and faecal larval output for the whole group are summarised in Graph 2. It is of interest to note that at the first

infection the peak level of complement-fixing antibody is attained when the infection is well on the wane as judged by faecal larval output. At the time when faecal larval output is maximal the antibody level is still quite low. Reinfection produces a more rapid and more elevated antibody response as might be expected.



GRAPH 2.—The faecal larval output and the serum antibody level in a calf infected three times.

The results of this experiment are summarised in Table VI. A strong acquired immunity was shown by all the animals in the groups. Clinical symptoms at the second and third infections as compared to the first showed a reduction consistent with the parasitological results of Table VI.

TABLE VI

FAECAL LARVAL COUNTS DURING THREE CONSECUTIVE INFECTIONS WITH *D. viviparus*

Calf No.	First infection	Second infection	Third infection	No. of worms in lungs at autopsy
	Maximal McMaster count/gramme	Results of Baermann Examination		
23	450	—	—	0
25	200	—	—	0
26	100	+	—	0
27	150	+	+	165*
28	225	+	—	6*
29	250	—	—	0
30	625	—	—	0
31	150	—	—	0
32	200	—	—	0
34	350	+	+	12*

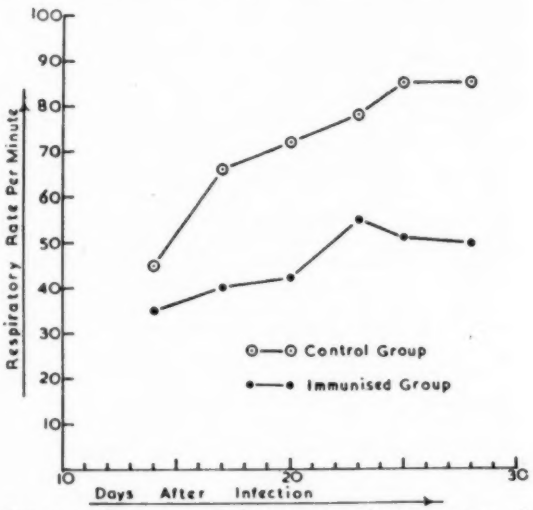
In a fourth experiment five calves were fed 300 larvae on each alternate day for a period of two months in an attempt to simulate a hypothetical "field" type of infection. Six months later four of these animals were challenged with 15,000 larvae each and the remaining one with 90,000 larvae. As in the previous experiment all the calves showed a high degree of acquired resistance.

(c) *Passive immunisation*

The next step in the immunological experiments was to see if the immunity conferred by an infection with *D. viviparus* could be transferred to a susceptible animal.

A number of recovered field cases of the disease were challenged with large doses of larvae as described under (a). Serum was collected about 30 days after challenge and a globulin preparation separated by sodium sulphate fractionation. A group of young susceptible experimental calves were each injected intraperitoneally with a total volume of 1,500 ml. of globulin solution in three divided doses. The immunised calves and an equal number of controls were then each challenged with 4,000 lungworm larvae and killed 30 days after infection. The results of this experiment are summarised in Table VII and Graph 3.

There is no doubt from these results that resistance to *D. viviparus* can be passively transferred.



GRAPH 3.—The mean respiratory rates in two groups of calves infected with 4,000 larvae, one group of which had been given hyperimmune serum.

TABLE VII

NUMBERS AND WEIGHTS OF LUNGWORMS RECOVERED FROM IMMUNISED AND CONTROL CALVES

	Calf No.	No. of worms	Total weight of dried worms (mg.)	Average D.M. per worm (mg.)
Immunised group	A*	60	—	—
	B*	0	—	—
	1	0	0	0
	2	0	0	0
	3	142	89·6	0·631
	4	49	16·2	0·331
	5	11	2·4	0·218
	Total	262	108·2	1·180
	Mean	37·4		0·536
Control group	C*	311	—	—
	D*	712	—	—
	6	1,224	906·6	0·741
	7	83	28·0	0·337
	8	1,131	890·6	0·787
	9	778	558·1	0·717
	10	1,262	1,362·8	1·080
	Total	5,501	3,746·1	3·662
	Mean	786		0·837

* These four calves constituted a pilot experiment carried out in essentially the same manner.

(d) *Active immunisation*

Because of the encouraging results of the passive immunity experiments and the solid immunity conferred by the natural infection, methods of protecting calves against lungworm by active immunisation were then investigated.

In the first active immunity experiment, 24 calves were divided into four groups. The calves of three of these groups were given courses of injections of an adjuvanted whole-worm antigen. The calves of the fourth group acted as controls. Each calf was challenged with 4,000 *D. viviparus* larvae and all calves were killed 30 days after challenge. The results of this experiment are shown in Table VIII.

TABLE VIII

NUMBERS OF WORMS FOUND AT AUTOPSY IN IMMUNISED AND CONTROL CALVES

Group	Calf No.	Injection (dates)		Challenge (date)	No. of worms found at autopsy
	1				91
	2				768
	3				676
A	4	22.6.55	20.7.55	20.8.55	685
	5				599
	6				826
				Mean	608 ± 242
	7				422
	8				34
B	9	22.6.55	—	20.8.55	694
	10				590
	11				245
	12				377
				Mean	394 ± 209
	13*				
	14				913
C	15	—	20.7.55	20.8.55	688
	16				174
	18				290
	19				374
				Mean	569 ± 308
	17				1,049
	20				588
	21				1,357
D	22	—	—	20.8.55	411
	23				443
	24				481
				Mean	688 ± 375

* Calf 13 died shortly after infection and is not included n this table.

The over-all result was disappointing in that there was no evidence that the course of vaccination had conferred any degree of protection against the challenge dose (the apparent reduction in "take" of group B as compared to the controls is not statistically significant). It was felt, however, that before abandoning this vaccination procedure a further experiment was desirable to determine the efficacy of vaccination against (i) smaller challenge doses and (ii) a challenge in the form of small repeated doses of infective larvae*. The 88 experimental calves were divided into four groups as shown in Table IX.

* This second experiment was carried out at the Agricultural Research Council's Field Station, Compton, Berkshire.

Half of the animals in each group received a course of two injections of adjuvanted vaccine with an interval of three weeks between injections. Six weeks after the latter injection all the calves were challenged. Autopsy was carried out 35 days after challenge. The numbers of worms obtained from the lungs at autopsy are recorded in Table IX.

TABLE IX

NUMBER OF WORMS FOUND AT AUTOPSY IN IMMUNISED AND CONTROL CALVES

Challenge	Vaccinated		Control	
	Calf No.	No. of worms	Calf No.	No. of worms
	596	60	589	—
	592	—	606	137
	600	—	594	330
	554	325	549	120
	555	90	545	450
Group A	570	—	573	590
	546	40	588	550
2,000 larvae	580	—	632	380
single dose.	526	147	527	—
	623	100	572	226
	556	200	609	180
Mean		123·1 ± 92·4		329 ± 162
	528	238	539	480
	622	123	522	203
	576	185	518	240
	544	73	599	277
	593	140	617	195
Group B	540	21	575	212
	621	128	634	164
2,000 larvae	532	140	605	333
administered	602	73	558	224
as 200/day	553	101	562	105
on alternate	531	0	587	312
days				
Mean		111·1 ± 65·4		250 ± 95
	586	40	578	96
	534	4	568	221
	581	42	533	105
	519	63	559	88
	585	71	571	94
Group C	629	120	550	53
	574	69	628	80
500 larvae	616	36	567	115
single dose	547	0	583	70
	612	93	633	2
	565	28	563	50
Mean		51·4 ± 34·6		88·5 ± 51·6
	552	8	607	69
	569	135	543	90
Group D	604	7	566	56
	564	24	584	83
500 larvae	541	23	536	111
administered	590	66	561	63
as 50/day	582	39	625	6
on alternate	608	22	517	65
days.	529	61	597	80
	598	1	635	56
Mean		38·6 ± 36·6		68·3 ± 26·5

There is a statistically significant reduction in "take" in all groups of vaccinated animals as compared to the appropriate controls. Although this result makes it clear that it is possible to confer some degree of protection by active immunisation, it seems likely that the method of vaccination employed here would be expensive and of limited value as a prophylactic against the disease in the field.

We have been investigating other methods of producing active immunity and one of these has been strikingly successful. The method was developed on the hypothesis that the stimulation of protective antibodies might be greatest when actively metabolising worms were used as the antigenic stimulus and also when such antigen was introduced at a site where maximum production of immunity would be achieved and where maximum effect on the parasite would be exerted. This site is, of course, the mesenteric node complex through which invading larvae must migrate.

Accordingly, methods of attenuating larvae were investigated, and one such method has shown very successful results. Final experiments on its efficiency and practical applications are being carried out at the moment and will be reported verbally at Congress. Over 1,000 calves are involved in a field trial of this vaccine at the moment, and a progress report on this experiment will also be reported at Congress.

Summary

In this paper we have attempted to outline briefly the reactions of the bovine animal to infection by *Dictyocaulus viviparus*.

The mechanism of production of clinical signs has been elucidated by a serial study of the associated pathology; this has clarified the hitherto unexplained and serious type of case which may occur in the pre-patent phase of the infection, the "fog fever" or sudden heart failure syndrome and the multiplicity of physical causes of the fully developed disease.

It has also laid a basis for the accurate diagnosis of the presence of infestation by histopathological methods.

The development of a quantitative complement fixation test has made possible the study of the serological response to infection. In a series of experiments involving several hundred calves reared in isolation the immunological response to various patterns of infection and immunisation has been worked out.

It is believed that a method of vaccination has been developed which confers a very high degree of protection against husk and there appears to be no reason why this should not be applied in the field in the near future. An account of its action under experimental conditions and in a field trial involving over 1,000 calves will be presented verbally at Congress.

Acknowledgments.—This work has been supported by a series of grants from the Agricultural Research Council.

We should like to express our gratitude to the veterinary surgeons of the west of Scotland for their co-operation in this work over the last five years. The photomicrographs are reproduced by kind permission of the Editor of the *Journal of Pathology and Bacteriology*.

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THE SPEAKER'S INTRODUCTION

Dr. Jarrett said: "In the short time we have to amplify the subject matter of the paper you have before you I would like to concentrate on prophylaxis and treatment.

"We have described the various stages in the study of the immunological response in this disease up to and including the attempts to induce active immunity by vaccination using freeze-dried adult worms. It became obvious that the best chance of obtaining a good degree of immunity would be by allowing larvae to migrate just so far and no farther, *i.e.* to let them get to the mesenteric nodes where they would stimulate antibody production but to prevent them getting to the lungs and there producing lesions.

"In other words we wanted attenuated larvae incapable of completing a life cycle. For this purpose we used X-rays.

"Since 1916 it has been known that X-rays have an adverse effect on *T. spiralis* larvae; and later, in America, it was shown that if rats are fed irradiated Trichinella larvae, an infection develops in which the adults are sterile and the rats subsequently develop a degree of immunity. This would be of little practical value in the common parasitic diseases with which we are concerned since the adult worms are largely responsible for the pathogenic effects.

"So we irradiated the pre-migratory stage in an attempt to find a dose of irradiation which would not allow development beyond the invasion of the mesenteric nodes. We started a series of experiments to try to find the dose of irradiation necessary to do this. In all we used 7 different levels which fortunately straddled the effective doses.

TABLE I

IMMUNISING EFFECT OF X-IRRADIATED LARVAE

Calf number	Immunising dose	Mean number of worms in those killed at 30 days	Challenge dose	Mean number of worms at autopsy
5—9	4,000 irradiated larvae (level A)	—	4,000	15.6
10—14		4.2		—
20—24	4,000 irradiated larvae (level B)	—	4,000	13.6
25—29		2.0		—
40—44	4,000 irradiated larvae (level C)	—	4,000	919.8
45—49		0		—
30—34	4,000 larvae	—	4,000	11.4
35—39		906.2		—
15—19	—	—	4,000	1,188.4

"In this table is illustrated an experiment in which 3 levels of irradiation were used. Levels A, B, and C. Now you will see from this that the procedure was to give each calf in the groups 4,000 larvae. This dose of larvae we knew from experience was capable, in the non-irradiated state, of producing clinical disease and subsequently a very strong immunity to re-infection. So we gave all the calves this number of larvae and killed half of them at 30 days to see whether any lungworms had matured. At this phase in normal infections all the worms should be in the adult stage when they are easily seen and counted. As you see here the results looked promising since only very small numbers of worms managed to reach the lungs in all groups.

" There was one snag, however. In Group A, although there were few worms there was quite a lot of lung lesions, and histological examination showed that many larvae had in fact reached the lungs but had diéd there, and there was quite a bit of reaction to them. These produced too many clinical effects to be acceptable as a field procedure.

" Groups B and C were better, Group B having only a few lesions and C none at all. In other words, the worms had been stopped somewhere *en route*. It then remained to find out whether any immunity had been conferred on the remaining calves, so after about 6 weeks they were challenged with 4,000 healthy larvae each. A non-vaccinated control group were challenged at the same time. Here you see the results. In the controls just over a thousand worms had matured. In Group C just about the same—no immunity here.

" But in Groups A and B there was a very greatly reduced take, indicating the development of a very strong immunity. Therefore Group B appeared to be the one to concentrate on since it produced minimum lesions during vaccination but conferred a good immunity.

" We then repeated these experiments at the B level and slightly above it and again got good results. But in order to pave the way for a field trial we attempted to find the minimum number of larvae which would give a reasonable degree of protection with the greatest safety and we settled for a quarter of the number used in the laboratory trials. This gave a good but reduced protection and the pulmonary lesions caused were minimal.

" From these systems of artificial challenge we took it to field conditions in two ways. First, through the co-operation of the local veterinary surgeons, we located a number of farms with histories of severe husk, the calves on these farms totalling about 1,000. On each farm half the calves were vaccinated and half left as controls. The animals have been faeces-sampled once per month since. No marked vaccine reactions took place and as far as the safety of the product went, everything seems fine. It is as yet too early to assess the protection conferred.

" The second method of field challenge was to turn artificially infected calves, 15 of them, onto a 3-acre pasture and follow them with 15 vaccinates and 12 controls; disease has already appeared in this field and 5 controls have died while there has been nó loss among the vaccinates.

" So, to summarise, it seems that vaccination against this disease may soon become a practical possibility. Tests for the life of the vaccine under storage conditions have been satisfactory and if the field trials turn out similar to the artificial experiments, it may be able to be marketed in the not too distant future.

" I would like to finish with a few words on treatment. The substances we mentioned in the text as having no effect on *D. viviparus* did not include the recently introduced I.C.I. products. We are at present conducting a field and experimental trial of these drugs and it is too early to assess their value. Three things must be borne in mind, however. One is that calves can die of husk in the prepatent period due to the pulmonary lesions produced by larval migration and it is not to be expected that a drug with a vermifuge action will greatly ameliorate the condition if the infecting dose has been very large; secondly, animals on an infected pasture are picking up larvae until the day they are treated or removed from that pasture and consequently have 24 days' worth of immature worms still to complete the life cycle, and treatment may have to be applied accordingly. Lastly, if treatment is started during the patent phase when the lesions we have described are well established, one should not expect too rapid a clinical improvement.

" In fact, under the conditions mentioned above we have been unable to prevent death in several calves using this drug. But if it removes even a proportion of the adult worms as claimed by the makers it will be a very useful addition to the veterinary therapeutic armoury; in fact the only drug so far produced to have any effect on *D. viviparus* at all. It does not remove the need for supportive therapy as outlined in the paper."

The Opener

Mr. W. H. Parker, in opening the discussion, said that he was very pleased to have been asked to do so, not only because of his interest in the subject but also because of his very high esteem for the Glasgow team responsible for producing the paper. That high regard was probably shared by most people in the room. Not only were the team remarkably capable as individuals but they had solved the problem of working as a team, thereby increasing their individual value many times.

The value of the Glasgow work was so well recognised that even their own innate Scottish modesty had not prevented the authors from hearing about it, and early in the paper were to be found four questions which, in the American language, might be referred to as $64,000 questions. Nevertheless, the writers had had no hesitation in claiming to have found the answers to all four of those questions. Were that true, they would indeed be a party of geniuses working together, but Mr. Parker feared he must disagree with the claim.

On the first question, the authors had gone a long way towards solving the problem of how the disease was carried over from one year to the next. In matters of that kind, positive evidence was significant, but negative evidence was often misleading, and it was very useful to have proved not only that carrier animals could exist from one grazing season to the next but also that the parasite could persist on the pasture over the winter.

Turning to question three, he could not agree at all that the authors had established suitable criteria for the diagnosis of parasitic bronchitis. They depended largely on larval counts, and in his experience calves could be dead from the disease in severe cases before the worms in their lungs were sufficiently mature for larvae to have appeared in the faeces.

On question four, the pattern of immunity, the Glasgow team were still working, and he was very glad that they were using field experiments to test their vaccine because no research work was fully completed without field experiments. The team were working to ascertain the answer to question four: it was a little early to say they had answered it.

Turning now to question two, the correlation between the clinical signs and pathological features, Mr. Parker wished to say right away that he considered a valuable contribution had been made in the pathological descriptions. Indeed, the work that had been done would be of great value to all the lesser lights, including himself, working in the same field. On the other hand, it seemed to him that the authors had been dazzled by the brilliance of their own work on the pathology and had attempted to project the results into the clinical field instead of trying to correlate the pathological findings with the clinical. Dr. Jarrett had somewhat modified that in presenting the paper that afternoon, but the paper tended to stress the damage after worms had reached maturity. In his own experience, the greatest damage was done before that stage was reached, and it must be while the larvae, and possibly the eosinophils, were migrating that the greatest lung damage occurred.

He wanted for the moment just to describe what he conceived to be the course of the disease. In the first place, increased respirations were the most characteristic feature and, in artificially induced parasitic bronchitis, commenced within about 7 days. Respiratory embarrassment would increase and coughing would, of course, occur, but the coughing was incidental and not so characteristic as the respiratory rate. In severe cases, the respiratory rate might be reduced when greater effort accompanied by an expiratory grunt occurred.

Fairly soon, in a matter of 4 or 5 weeks from the administration of the larvae, a crisis was reached and that picture also was recognisable in the field. In severe cases deaths might occur until the time of the crisis and then quite suddenly the surviving calves would start to improve. In relatively mild cases, in which no deaths occurred, there was equally a sudden change and the calves began to improve.

In experiments it had been shown that the live-weight gain was only temporarily impaired in those mild cases,

though the clinical picture might be rather alarming for a time. What was to be stressed was the fact that there was not a very great difference in the number of larvae required to produce the mild case on the one hand, and the severe case with death on the other.

That led to the question of administration of larvae. While the Glasgow team claimed to have the only satisfactory method, Mr. Parker and his colleagues considered the Baermann technique quite satisfactory, but he would be quite unhappy in administering larvae by drenching. They always used the stomach tube. The claim that the degree of effect could be estimated in advance by the number of larvae administered ignored other important features, namely, the age of the calves, the weight, the breed, the nutritional level, and even the individual idiosyncrasy—all matters of considerable importance.

Turning to the question of treatment, the authors claimed to have tested 20 different substances, all of which were of no value. That was a remarkably useful piece of information and it was said that they had not stated what those substances were. He appealed to them to make that information public.

The authors advised taking calves inside and feeding them well. The idea of feeding well was a sound and generally accepted practice in combating any parasitic disease, but, in view of Michel's work on immunity (1956), it seemed quite pointless to advise taking the calves inside. Such a method of treatment had no more justification than the archaic one of putting a calf's head in a sack with iodine on a hot brick.

Surprisingly, the authors made no reference to the use of phenothiazine, which was often very sound practice where husk occurred because of the time-honoured principle, appreciated only too late by Hitler, that a war on two fronts was to be avoided if possible.

Mr. Parker believed that, until recently, the only controlled experiment reported, in which success in killing worms was found, was dealt with in the paper on Husk which was presented to the British Veterinary Congress exactly 20 years previously by R. H. Smythe (1937), in which he characteristically stated that the chief merit of most means of attacking husk worms had been the complete inefficiency of the drugs used. Smythe had gone on to describe a controlled experiment, in which oil of chenopodium was used intratracheally, and in which 4 calves treated with that drug died within a few hours due to the fact that all the worms had also been killed. In the other group, the 4 calves, and presumably their worms, all survived.

Mr. Parker had himself been carrying out some experiments in the treatment of husk with diethylcarbamazine (Parker, 1957), and as that was presumably the reason for his being asked to open the discussion there was no need for further apology for introducing the subject. Briefly, it had been shown that that drug, if given early in the disease, would result in a rapid reduction of respiratory rate within two days of the commencement of treatment. There were extremely few larvae in the faeces of the calves so treated, and if controls died, the treated calves not only survived but also thrived.

The following photographs indicated the effects of the drug:—

The first photograph showed the worms recovered from 4 calves which were killed 21 days after the administration of larvae. The two on the left were untreated; the two on the right were treated for three days commencing on the 14th day. The second photograph showed the position when treatment and slaughter had been delayed one week. The effect was nothing like so marked and it remained to be worked out how the drug should be used somewhat later in the disease as in this case.

In conclusion, Mr. Parker stressed the tremendous importance of controlled experiments in a disease in which spontaneous recovery could occur with such suddenness. That outstanding feature of the disease had been and would remain a source of profit to those whose commercial interest in drugs exceeded their interest in animal health. (Applause.)

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The General Discussion

Dr. E. L. Taylor (Weybridge) said: "In the first place I should like to say how greatly I appreciate the energy and unity of purpose of this group of workers and how greatly I have enjoyed those few occasions on which I have been privileged to spend a day in their laboratories and there see the team spirit working at its best. There are, however, one or two general comments that I should like to make on this Congress paper. In the first place, as I have been interested for some years in the epidemiology of parasitic diseases and have been preaching a gospel that they are very largely to be attributed to man's interference with natural ecological conditions, I can hardly agree with the title which refers to the *natural history* of a parasitic disease, which according to my gospel is an unnatural occurrence. I would agree, of course, with a reference to the 'natural history' of the parasite but would prefer the 'epidemiology' of the disease.

"The second point concerns specialisation. There must be a number of specialists in this room of one kind and another, and I suppose there to be a greater proportion of specialists attending every successive Congress—although Cambridge must be exceptional in that respect, being a breeding ground for such people. At this present meeting I feel it to be necessary for someone to speak in defence of the specialists.

"I have been a little interested in the subdivision of research work in the veterinary field and in the classifications of specialisations and have always found a difficulty in placing the pathologist. As a specialist I suppose he is usually a histopathologist, a man with a particular knowledge of the changes in cells and in tissues as a result of disease. Here, at this meeting, however, we have a report of very good work, showing notable advances in what has been regarded as the field of specialisation for the parasitologist and one wonders what it is that led the pathologist to succeed where the parasitologist failed—but more of that later.

"At the moment, speaking as a specialist in helminthology I should like to say that in my opinion this paper goes a little astray in the emphasis placed on one or two points. Incidentally, I feel it would have added to the value of the paper to include a brief section outlining the foundation on which the authors have built, and referring to previous work in the field. It seems to me that among the most important points recently added to the knowledge of this disease was the recognition of the inhibition of larval development within the body of the host animal and the very common occurrence of silent carriers, which provided a much needed explanation for the annual reinfection of pastures.

"Another point in which there also seems to be a misplacement of emphasis concerns the duration of the life of larvae in the pastures. The peculiarity of these particular larvae is that they are short lived. What does not seem to have been recognised by these workers is that the disappearance of larvae from the pastures follows the exponential curve, and that the point in the long tailing-off period at which living larvae can still be recovered refers rather to the methods used in the observations than to the longevity of the larvae. If a very large amount of heavily infected faeces is placed on a very small area of ground, or if a large number of larvae are exposed under what happen to be favourable conditions—as for instance in pots of soil on the roof of a building—the end point of survival can be shown to be delayed. It is at least as important to know what usually happens on actual pastures where the ten-millionth larva is less likely to be recovered by grazing cattle, and that although it is possible for cattle to become infected through the grazing of spring pastures the much more likely source of infection is the carrier animal that reinfects those pastures.

"The discovery of the vaccine could be regarded as the most interesting part of the work as well as the most severe blow to the specialists. Most of the surprise discoveries are accidents that are subsequently rationalised, and this is no exception. I think it may be said without fear of contradiction from the specialists that no one who had been really soaked in the literature of helminthology would have set out on a large-scale experiment aiming at the control of a parasitic disease by the use of a vaccine. I must admit that I regarded some of these large-scale experiments on large farm animals as most unlikely to succeed. Fortunately nothing was said, and I have no words to eat, but such was the case. I must conclude, therefore, from the successful outcome of this work that there is an occasional disadvantage in having been nurtured in a specialist tradition and an advantage in making a new approach from first principles.

"A little earlier in the course of these remarks I said that it was not easy to recognise the field of specialisation for the pathologist in the investigation of disease. Is this one of his functions—to make a fresh start where specialists appear to hang back and occasionally to spring a surprise? Should we perhaps employ this method more frequently?

"We cannot admire too much the energy, the co-operation, and the enthusiasm that has speeded this present work on to such a satisfactory conclusion. These workers are to be most heartily and most sincerely congratulated."

Mr. W. E. Parish (Weybridge): "I wish to congratulate the authors, not only for writing a very stimulating paper and on making such progress in a condition that is of immediate importance to the practitioner, but also an account of the additions they have made to our knowledge of the study of the effects of an actively metabolising parasite on its host rather than a study of two entities, host and parasite. With reference to this progress I would be grateful if the authors would enlarge certain points arising from their paper.

"I noted that when 50,000 infected larvae were fed to disease-free calves, that by the 16th to 18th day an acute fatal condition resembling 'fog fever' resulted; whereas those dosed with 5,000 larvae developed clinical but not fatal husk, and the lesions in the final stage are described as being qualitatively different. Do the authors believe that this results solely from the larger number of larvae causing mechanical damage to the lungs, or, as the 'fog-fever type' syndrome has so long been associated in people's minds with some form of allergy, that following the penetration of the larvae into the mesenteric nodes on the third day of infection that an antibody response is elicited and sensitisation of the lungs may occur in the ensuing 13 to 15 days, so that the continued presence of the antigen in the larvae, may also be partly responsible?

"On one minor point I would venture criticism. Hyaline membrane formation in the walls of the alveoli is described as resulting from the evaporation of oedema fluid leaving a film of coagulated plasma protein. However, hyaline membrane formation may be seen in many other conditions and other species, *e.g.* rheumatic pneumonitis, and the vernix caseosa of pneumonia of the new-born in man. In some of these conditions it is not always possible to detect the presence of any oedema and there is good evidence that the membrane in some forms of rheumatic pneumonitis may be formed solely from the fusion and degeneration of septal cells, and in pneumonia of the new-born, the presence of desquamated epithelial cells is held to be every bit as important in the formation of the hyaline membrane as the vernix caseosa. As hyaline membrane formation may occasionally be seen in the lungs of clinically normal cattle following prolonged transit in cold weather without any oedema being found macroscopically, or by histological examination of paraffin or frozen sections, I suggest we should remember that such membrane formation may be the result of other factors than deposition of plasma protein's following hyperventilation of oedematous lungs.

"In the clinical diagnosis mention is made of the syndrome '"fog fever" as it occurs in adult animals,' and your histological examinations of *post-mortem* material with one exception revealed the typical picture of husk. Does this mean that larvae were actually seen in these lesions, or does it refer to the type of lesion? For it is possible to sensitise calves with other materials and produce a similar pulmonary lesion, but which is not due to dictyocaulus infection.

Would you, in general terms, say anything about the relative antibody titres as measured by complement fixation, just prior to challenge, in those animals that had recovered from a natural infection or experimental infection and that subsequently proved to be resistant to challenge, and those calves that had been vaccinated with adjuvanted worm material and proved more susceptible to challenge.

"Finally, on a point of historical accuracy, though I may have misunderstood your statement in the introduction of your paper, the fact that the lung damage and clinical symptoms of husk were due to invasion of the pulmonary tissue by the larvae and not due to the mechanical obstruction of the bronchioles by adult worms, is not a recent discovery, but was recorded by Dr. Taylor in 1952."

Dr. E. J. L. Soulsby (Cambridge): "I wish to congratulate the speakers on their paper which has to a great extent given a new outlook to the problem of husk.

"The advent of a vaccine for husk should have great repercussion on this disease and it is pleasing to see that at last the large amount of work which has been carried out on small animals with regard to immunity to parasites has now been translated into a practical proposition.

"One point of epidemiological importance needs to be emphasised with regard to this vaccine. Since the vaccine depends on the irradiation of larvae so that they are unable to reach the mature state it follows that immunity is allowed to develop without fear of patency. This is in distinction to that occurring in natural conditions where patency of at least a few worms occurs and transmission of larvae occur, these being available to other animals. Thus both from the individual aspect and from the group aspect this vaccine has many advantages.

"I would further like to re-emphasise a factor which has been lost site of recently, and that is that in parasitic bronchitis one frequently has a concomitant heavy burden of intestinal nematodes. In the past due recognition was taken of this factor and suitable treatment was adopted. I feel that general practitioners should return to consideration of this factor."

The Replies

Dr. Jarrett, in replying to the discussion, thanked the opener for his kind remarks. It should be emphasised that the paper was only a summary of the work which had appeared or was about to appear and it omitted a great deal of detail. The fundamental point in any of the work was the infectivity of larvae. Information on the Baermann method of culture which had been published in this country or in America showed very little correlation between magnitude of infection and "take" and indicated a very high mortality rate among the larvae. Some workers administered as many as 50,000 larvae and produced very mild reactions.

Drenching could be done effectively and safely and there was no need to use stomach tubes. The authors would be quite willing to publish information on facts referred to in the paper.

The question of fog fever was controversial and it was not the intention of the authors to go into it at all deeply. It was not being claimed that parasitic bronchitis was the only cause of fog fever; most cases of fog fever appeared to be associated with acute heart failure. Although severe pulmonary oedema might not be always demonstrable at *post mortem*, it was assumed to be a prerequisite of hyaline membrane. The heart suffered from anoxia, which gave rise to pulmonary oedema, and that in the presence of dyspnoea produced hyaline membrane formation. A vicious circle was started and that was why animals died very suddenly. The same sort of thing occurred in human beings with rheumatic fever.

In the matter of retardation of development, the authors had not come across the type of phenomenon mentioned by Dr. Soulsby in the type of experiments that had been carried out. Most of their work in the study of tissue reactions to parasites was histological. It appeared likely

that an exaggerated reaction to the irradiated larvae took place in the mesenteric nodes and that antigen was trapped and held for a time almost like an adjuvanted vaccine.

It was true that phenothiazine was not referred to. Thousands of samples of faeces had been examined and, strangely enough, parasitic gastroenteritis was seldom encountered. The system of husbandry employing permanent pasture was much less common in the west of Scotland than in southern England.

The reason why the literature on parasitic bronchitis was not reviewed was that an attempt was being made to present a consecutive study of the development of the disease and its immunity in as simple a way as possible without introducing controversy and qualification at all stages. The views of other workers would be fully discussed in the more detailed publications. The greater part of the ecology of the organism on pasture was not referred to; Dr. Taylor's colleagues had done excellent work in this field but it was outside the scope of the various specialists in the present team.

Dr. W. I. M. McIntyre, in reply, said that the authors owed a great deal, both directly and indirectly, to Dr. Taylor. The controversy that had taken place between them and him from time to time had proved helpful and assisted in pushing them on in the struggle. Dr. Taylor's first two points were answered by his third. The trouble in certain fields was that the histopathologist had not been given his day and there existed a need for much greater co-operation.

Dr. W. Mulligan, in reply, said it would be too much to hope that the complement fixation test indicated the measure of protective antibody. The levels of antibody determined reflected some of the things going on in the animal. Someone had produced the analogy of creatures which lived in caves and were unable to live outside them: their ideas of the outside world were formed from the shadows they saw created. A similar principle applied to the serology dealt with in the paper. It was extraordinarily useful, of course, in certain instances for assessing whether the animal had been in contact with the disease.

When levels of irradiation were used which were so great that they caused the larvae to be killed, assumptions were substantiated by serology because there was no secondary response. The normal behaviour of an animal which had been in contact with parasitic bronchitis previously was to show a clear indication of it.

The Pathological Differentiation of Diseases of the Central Nervous System of the Pig

By

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PROBABLY no species of farm animal is afflicted with nervous disease to a greater extent than the pig and in none is diagnosis on a purely clinical basis more difficult for the general practitioner. Furthermore, owing largely to the difficult of restraining pigs adequately, clinical pathological methods such as the examination of the cerebro-spinal fluid are unlikely to be of much assistance to the practitioner. Treatment of the individual animal is, however, rarely of consequence compared with the need to reach a diagnosis on which therapeutic and prophylactic measures designed to protect the group or herd as a whole may be based so that, in an outbreak of disease, one or more animals are usually available for autopsy.

It is against this background that the pathological differentiation of the diseases of the central nervous system of the pig is considered here and it is emphasised that the gross and histological examinations of the C.N.S. are not a substitute, but are complementary to whatever clinical, bacteriological, biological or other tests are available. In cases where the latter are specially indicated on grounds of specificity and/or speed they will usually be the diagnostic aids of choice, though clearly they are of limited use when they give a negative result.

Since, apart from the paper by H. C. Smith (1955), there is no comprehensive review of the subject in the English language, an effort has been made to cover the whole field of diseases of the central nervous system. Though a critical review has not been attempted some conditions which have been recorded in the literature have been omitted as being inadequately defined or substantiated. On the other hand, conditions recently described have been included when they appear to be valid.

Diseases known to occur only outside Great Britain have been included in Table I (where they are indicated by an asterisk *) for the sake of completeness and are discussed in the text where they have a bearing on conditions already recognised in this country; but in the main the author has restricted himself to the nervous diseases of British pigs, his experience being based on the examination of approximately 2,000 cases of experimental or naturally occurring disease submitted to Weybridge during the past 7 years.

TABLE I

PATHOLOGICAL DIFFERENTIATION OF THE DISEASES OF THE CENTRAL NERVOUS SYSTEM IN THE PIG

A.—Inflammatory Lesions of the Brain and Cord

(1) *Non-suppurative conditions*

(i) *Caused by viruses*

(a) *Viruses affecting nervous tissue primarily*
- *Rabies
- *Teschen Disease
- Talfan Disease
- *Poliomyelitis suum
- *Portuguese encephalomyelitis of pigs
- Aujeszky's disease
- Louping Ill
- *Japanese B Encephalitis

(b) *Viruses affecting mesodermal tissue primarily*
- Swine fever
- *African virus disease of pigs
- *Haemagglutinating virus of Japan (H.V.J.)

(ii) *Caused by protozoa*
- *Trypanosoma brucei
- Toxoplasma gondii

(iii) *Focal lesions of unknown cause*

(2) *Suppurative conditions*

(a) *Diffuse*
- Streptococcal choriomeningitis (Diplococci)
- Streptococcal meningitis
- Escherichia coli septicaemia
- Glasser's Disease (infectious serositis and arthritis)
- Salmonellosis
- Swine erysipelas
- *Leptospira pomona infection

(b) *Local*

Listerella, Pasteurella, Corynebacterium pyogenes, Brucella sp. } Abscess/spondylitis/osteitis

Streptococcus, Staphylococcus } multiple septic emboli

(3) *Tuberculosis*

B.—Degenerative Lesions of Brain and/or Cord

(1) *Characterised by malacia*
- Infarction
- Transverse myelitis
- Local myelomalacia
- Polioencephalomalacia
- Meningoencephalitis eosinophilica
- Cerebrospinal nematodiasis

(2) *Characterised by demyelination without malacia*

(i) *Toxic*
- Uraemia
- Organo-phosphorus compounds

(ii) *Nutritional*
- Pantothenic acid deficiency
- Pyridoxine deficiency

(iii) *Unknown*
- Enzootic ataxia
- Neonatal spinal demyelination

C.—Mechanical Effects

(1) *Trauma*
- Vertebral fracture
- Foreign body

(2) *Pressure*
- Vertebral dislocation
- Dislocation of intervertebral disc.

* Names indicated thus are infectious diseases not known to occur in Britain.

Hydrocephalus
Intracranial haemorrhage
Tapeworm cysts
Arachnoiditis
Tuberculoma
Neoplasia < External
Internal < Neural
Non-neural

D.—Vascular Accidents and Disease

Haemorrhage
Vascular rupture
Arteriolar disease
Purpura
Cerebellar haemorrhages of Vit. A deficiency
Thrombosis
Endarteritis obliterans
Periarteritis
Arachnoiditis
Infarction

E.—Neoplasia

(1) *Neural*
Glioma
(2) *Non-neural*
Lipoma. Chondroma. Myxoma Fibroma
Lymphoblastoma

F.—Developmental Abnormalities

Partial reduplication (*e.g.*, Diprosopus thoracopagus)
Cyclopia
Hydrocephalus
Meningocoele and Meningoencephalocoele
Porencephaly
Microgyria
Aplasia of cerebellum
Purkinje cell abnormality (Seibold and Roberts)
Diastematomyelia
Pigmentation of cerebellum
Trembles (myelinogenesis imperfecta neonatorum)
Spina bifida

G.—No Lesions Known

(1) *Bacterial toxins*
Tetanus
Botulism
Oedema disease
(2) *Poisons*
Many
(3) *Unknown*
Congenital paralysis
Idiopathic epilepsy

Table I is an attempt to provide a working classification of the diseases of the C.N.S. of pigs, based on the type of lesion and (where known) the causal agent, and is intended mainly as a framework within which the differentiation of the conditions catalogued may be discussed. In view of the limitations placed on the length of this paper some conditions are mentioned by name only, but in the case of some of the more exotic, references have been included.

Some conditions will be seen to appear more than once in the Table, but it is felt that the possible confusion will be compensated for by the greater completeness of each section.

Methods

As already explained we have been concerned very largely with animals already dead, and in most cases with tissues already preserved. It is the author's contention that in the foreseeable future there will be little or no place for examination of the C.S.F. of the pig as a diagnostic, as distinct from a research tool, and therefore no attempt will be made to discuss it, though the interested reader is referred to Hankhauser and Wyler (1953) and Fischer and Starke (1951).

As a routine, pig tissues taken at Weybridge or sent in from the Veterinary Investigation Centres are preserved in 10 per cent. formol saline in 1 lb. screw-capped jars, and histological techniques are adapted to this fixative.

Blocks are taken from the C.N.S. as follows:—

T.S. Anterior Cerebrum through the corpus striatum, the landmark being the middle of the tuberculum olfactorium.

T.S. Anterior Corpora Quadrigemina taken at the highest point of the hemispheres.

T.S. Medulla at the level of the obex.

L.S. Cerebellar vermis (or failing that a T.S. through the middle of the organ).

T.S. Lumbar enlargement of cord.

L.S. Two or more Dorsal Root Ganglia from Lumbar region.

Routinely, paraffin sections are stained by Haematoxylin and Eosin, and Loyez method is used as a positive method for myelin, and Marchi's method or Glee's modification for degenerating myelin.

Though in suitable cases they may be supplemented by others, the above blocks now constitute the Weybridge discipline for examining pig C.N.S. and it is our experience that they constitute the irreducible minimum from which a differential diagnosis can be expected in difficult cases, though many conditions can be diagnosed with confidence on the brain sections alone. Naturally it is a great asset in choosing blocks for examination to have a description of the clinical signs observed in life, but in some cases this can be misleading and all too often the clinician is unable to suggest the possible location of the lesion or even give a clear account of the animal's movements.

Inflammatory Lesions of the Brain and Cord

The primary productive inflammatory conditions of the C.N.S. (which are virtually synonymous with the infectious diseases) have been arbitrarily classified into a suppurative group (exclusively of bacterial origin) and a non-suppurative group (largely, but not entirely, the result of viral infection) and tuberculosis.

Macroscopically meningitis is not evident in the non-suppurative meningo-encephalomyelitides while it usually is in the purulent conditions. In tuberculous meningitis the greyish nodular granulomatous lesions of the arachnoid are said to be characteristic.

Virus infections are differentiable microscopically from suppurative conditions by the absence of purulent exudate and may be further divided into those primarily involving the ectodermal elements or nervous tissue proper and those affecting principally the mesodermal (vascular and microglial) elements. The latter group will be dealt with first, chiefly because it comprises the most important of the nervous diseases affecting pigs in Britain but also because it provides a pattern with which the other non-suppurative encephalitides may be compared.

NON-SUPPURATIVE CONDITIONS

Swine Fever

The high incidence of lesions of non-suppurative encephalitis in cases of swine fever and their probable utility as an aid to diagnosis were recognised independently and almost simultaneously by Dide (1930) and by Seifried (1931, 1932 a & b). Since that time their observations have been confirmed by a number of investigators (Bendinger, 1934; Salvalaglio, 1937; Helmboldt & Jungherr, 1950 and 1952; Sassenhoff, 1952; Ressang, 1953; Englert, 1953; Ohbayashi, 1953; and Pallaske & Kretzschmar, 1955) though a few workers have expressed doubts as to the specificity of the lesions described. (Kobe & Schmidt, 1934; Jones & Doyle, 1953.)

The typical lesions of swine fever as described originally by Seifried in Germany and later by Helmboldt and Jungherr in U.S.A. and as seen by us in Britain is a pan-encephalitis with a variable and usually very mild myelitis. Medulla, pons, corpora quadrigemina and thalamus are most conspicuously affected but the cerebrum and to a lesser extent the cerebellum are also involved. Infiltrative lesions are present in both grey and white matter, though the relative sparing of the cerebellar cortex (in contrast to the Teschen-Talfan-Poliomyelitis suum group) and of the cerebral cortex (in contrast to Aujeszky's disease) is usually marked, and the over-all impression is that the incidence of lesions in the white matter is higher than in the grey. The over-all histological picture may best be imagined as a delicate network of susceptible and highly reactive mesoderm, spread over a matrix of ectoderm not itself susceptible to the virus but highly sensitive to any interference with its nutrition and hence with its blood supply.

The endothelial lining of the blood vessels is constantly and obviously affected and this is especially marked in the precapillaries. Swelling and degeneration of endothelial cells occurs together with attempts at proliferation. All changes from slight hesitancy of the endothelium through swelling to frank necrosis are usually visible together with simultaneous attempts at regeneration. The lumen of the vessels becomes irregular and narrowed and its wall swollen, oedematous and infiltrated with round cells producing the so-called "vascular cuffing." Haemorrhages into the wall of the vessel or the perivascular tissue may be seen. As the damage is primarily vascular, cuffing of the vessels is, of course, present in the leptomeninges and choroid plexuses also. Proliferation and migration of microglial cells is evident particularly in the neighbourhood of blood vessels and in the periacquaductal and periventricular tissues producing conspicuous glial clumps.

Partial or complete thrombosis of vessels may be evident in a small proportion of cases, but it is usual for the effect of an impaired blood supply on the health of the neurones to be seen in virtually all cases which end fatally. These changes, margination of nucleus, satellitosis, chromatolysis and di integration of the nucleus are, however, of too frequent occurrence in pigs dying of other diseases to have any particular significance in relation to the diagnosis of swine fever. No inclusion-bodies have been seen.

The criteria we have employed for the recognition of swine fever in the C.N.S. are as follows: There should be an unequivocal non-suppurative panencephalitis, involving at least the cerebrum, corpora and medulla and characterised by vascular cuffing (with marked endothelial damage) and usually focal and/or diffuse microgliosis. On this basis one may expect to identify some 90 per cent. of outbreaks of swine fever on the examination of a single brain, while if two or more animals from the same outbreak were available the percentage could be expected to approach 100.

Factors influencing the incidence and appearance of lesions

(1) Stage of Disease. Lesions have been seen in pigs killed as early as 5 days after experimental infection, but are not usually well developed until about 10 days and are most marked in animals which have been allowed to die of the disease. For this reason, it is usually inadvisable to kill a pig for neuropathological examination unless clear nervous signs are already present.

(2) Effect of Crystal Violet Vaccination. Though Potel (1955) has described a cellular reaction in the brains of pigs vaccinated with crystal violet vaccine, Done and Doyle (1951) failed to find lesions in pigs which received 40 c.c. of vaccine, and it is the author's opinion that the presence of a cellular reaction following vaccination is an indication that either the virus in the vaccine was not completely inactivated or that the animal was already infected when vaccinated.

However, the effect of previous crystal violet vaccination can be seen on the development of lesions in a pig which subsequently contracts an overwhelming swine fever infection. In these cases glial proliferation is rare and the vascular lesions, though widespread, are in the main less severe than those in unvaccinated pigs. In the absence of a history of vaccination some of these cases can be difficult to interpret.

(3) Effect of attenuated virus. Lapinised swine fever vaccines normally produce a minimal response in the brain of vaccinated animals, but in those pigs in which the vaccine produces a severe systemic reaction culminating in death, the lesions in the brain do not differ materially from those produced by "wild" virus.

It is the author's opinion that neuropathological examination provides a very useful aid to the diagnosis of swine fever. False negative and doubtful diagnoses, together total only some 10 per cent. while under British conditions, and with some experience, false positives should be very small in number. The following are the most common difficulties in differential diagnosis:—

(a) The presence of heavy cellular accumulations (simulating "round cells") round the lateral ventricles and locally in the cerebral cortex. These are completely normal as will be apparent if blocks are always taken from the same part of the brain.

(b) The vague endothelial swelling and sparse perivascular infiltrations sometimes seen in toxic conditions and salmonellosis. Microglial reaction is absent and so usually is endothelial proliferation.

(c) Odd foci of microgliosis, occasional cuffed vessels, or local paravascular clusters of round cells in the leptomeninges, particularly over the cerebrum. In the main their cause is unknown and they are not regarded as suspicious of swine fever unless in type and distribution they satisfy the criteria given above.

(d) Of the other non-suppurative encephalomyelitides known to occur in Britain, all those of virus origin produce primary lesions in the grey matter and usually severely affect the spinal cord, while meningoencephalitis eosinophilica is distinguished by its local distribution and spectacular perivascular eosinophile infiltration.

African Virus Disease of Pigs

This condition, also called African Swine Fever though it is apparently unrelated to swine fever, produces a non-suppurative vasculitis in the brain (Hudson & Done, 1951) which is much less severe and extensive than that usually found in swine fever.

Haemagglutinating Virus of Japan (H.V.J.)

For details see Ishitani *et al.* (1954) and Sasahara *et al.* (1954).

Rabies

Rabies is diagnosed on the presence of Negri bodies in neurones, coupled with biological examination of brain from a suspected animal. Its histological differentiation from Teschen disease and swine fever is dealt with by Michalka (1942).

Louping-ill

Louping-ill, though widely present in sheep in Britain, has not been reported in pigs for over 30 years and the only published descriptions of its histopathology in the pig concern experimental infections (Brownlee & Wilson, 1932). Until detailed comparative work has been done the author believes that it is virtually impossible to distinguish it on purely histological grounds from Teschen disease, Talfan disease and Poliomyelitis suum, so that differential diagnosis must rest on the isolation of virus in mice or embryonated eggs from acute cases, or the demonstration of louping-ill antibodies in convalescent animals.

In the author's limited experience of the experimental disease in pigs it seems that the cellular reaction is concentrated round individual neurones to a much greater extent than in the other virus encephalomyelitides.

Talfan Disease

This condition, recently described in Britain by Harding, Done and Kershaw (1957), is a polioencephalomyelitis of virus origin characterised in its acute phase by heavy focal microgliosis and vascular cuffing in both grey and white matter of brain and cord though the grey matter is much more severely involved, and in the chronic stage by more or less symmetrical demyelination of the dorsal bundles of the cord and to a lesser extent of fibres in the ventral and lateral funiculi. The inflammatory lesions are particularly prominent in the molecular layer of the cerebellar cortex, in the dorsal and ventral horns of the cord, especially in the dorsal and lumbar enlargements and in the dorsal root ganglia which are spectacularly infiltrated with round cells and some groups of eosinophiles. Patchy meningitis is present in the interfoliar clefts of the cerebellum but elsewhere meningeal infiltration is relatively mild. Animals recovering from an attack suffer a loss of neurones which may cause residual nervous signs.

Though it can be distinguished with relative ease from swine fever it is virtually indistinguishable histologically from Teschen disease, Poliomyelitis suum and louping-ill. The sensory demyelination of Talfan disease has not been described in the other three conditions nor apparently has a ganglionic infiltration been remarked upon in louping-ill in the pig, but careful comparative work on all the conditions by the same group of workers will be needed before these apparent differences can be regarded as significant.

Poliomyelitis Suum

Poliomyelitis suum (Bendixen & Sjolte, 1955) may well be the same as, or related to, Talfan disease, but at the moment they differ in their published descriptions in respect of age incidence and histological lesions, though these may well be a reflection of different approaches by different groups of workers.

Portuguese Encephalomyelitis of Piglets

A condition described in Portugal by Tropa and Correia Madeira (1954) resembles Teschen disease closely, but like Talfan disease and Poliomyelitis suum differs epidemiologically from the classical disease seen in Central and Eastern Europe and in Madagascar.

Teschen Disease

This disease (for histopathology see Horstmann, Manuelidis & Sprinz, 1951; Fankhauser & Wyler, 1953; and Manuelidis, Sprinz & Horstmann, 1954) differs from the three preceding in its greater clinical severity and higher mortality, but it is felt that at present it cannot otherwise be differentiated.

Fischer and Starke (1951) have recorded the changes in the C.S.F. in 78 experimental cases and Fankhauser and Wyler (1955) have also given some figures, but in the absence of reliable values for normal pigs and pigs suffering from other nervous diseases they are of little practical value.

Aujeszky's Disease

Though to date only one outbreak of Aujeszky's disease in pigs has been definitely confirmed in Britain (Anon., 1954) the condition is frequently suspected on clinical grounds and is known to occur sporadically in Ireland.

The normal portal of entry is believed to be the nasal mucosa (Shope, 1935) and the virus spreads

neurotropically, probably by way of the tissue fluid spaces rather than along axis cylinders as in experimental herpes in rabbits (Boyse, Morgan, Pearson & Payling Wright, 1956); these two theories at least appear adequately to explain the distribution of lesions in the C.N.S. of naturally affected pigs. In the cases seen by us the cerebrum and cerebellum have been constantly and severely involved with progressively less spectacular damage in the midbrain, medulla and spinal cord, this differential being most apparent in animals killed before the natural termination of the disease. The disease is a polioencephalomyelitis which may be distinguished from the other conditions described by the occurrence of foci of frank necrosis in the grey matter with a proportion of polymorphs in the cellular exudate and by the presence of characteristic intranuclear inclusions. Though Hurst (1933) was unable to find any inclusions in his series, Shahan, Knudsen, Seibold and Dale (1947) demonstrated their presence in experimentally affected pigs and Done (1955) has confirmed that they occur in the natural disease also. The inclusions are sometimes difficult to see in normally stained H & E sections but can be emphasised by deliberate overstaining with eosin. They occur most frequently in the cerebrum and with much less frequency in the Purkinje cells of the cerebellum, but rarely in the more caudal parts of the C.N.S. Herpes simplex which is related immunologically to Aujeszky's virus and produces similar intranuclear inclusions in rabbits is apparently non-pathogenic for the pig even by intracerebral inoculation (Done & Harding, 1956). The presence of Aujeszky's disease can be confirmed by the isolation of the virus in rabbits from fatal cases or the demonstration of virus neutralising antibodies in the sera of recovered pigs.

Japanese B Encephalitis

For references and details see the review by Ochi (1953) and Experimental Report No. 30 of the National Institute of Animal Health, Tokyo, Japan, 1955.

Protozoal Diseases

Toxoplasma gondii is known to occur in Britain, has been demonstrated in pigs (Farrell, Docton, Chamberlain & Cole, 1952; Sanger & Cole, 1955; and Momberg-Jorgensen, 1956) and recovered from the brain (Farrell *et al.*, 1952) but so far no histological description of the reaction produced by the brain to it is available, though it is possibly similar to that in dogs.

Trypanosoma brucei infection produces a non-suppurative vasculitis in pigs (Glasser, 1950; Fankhauser & Wyler, 1953).

Suppurative Conditions

(a) *Diffuse meningoencephalitis and myelitis.*

The streptococcal choriomeningitis and arthritis described by Field, Buntain and Done (1954) is characterised by a fairly strict age incidence of 2 to 6 weeks (usually 4 to 6 weeks) and the presence of a diplococcus α-haemolytic on sheep blood agar. Pathologically the choroid plexus of the fourth ventricle is always involved and meningitis tends to be less marked than the choroiditis.

There also exists in Britain another streptococcal meningitis syndrome usually involving pigs of 2 to 4 months of age in which the organism (also so far untyped by the Lancefield system) resembles *Strep. bovis* in its biochemical characters except that it ferments raffinose. Streptococci in chains are found in the pus and the meningitis appears to be more constant and severe than the choroiditis.

Apart from Glasser's disease (infectious serositis and arthritis) which is not very frequently diagnosed in Britain but in which a diffuse purulent leptomeningitis occurs in 85 per cent. of cases (Hjärre & Wramby, 1943) the principal other condition in which we have encountered a diffuse purulent meningitis is in coliform septicaemia of early-weaned pigs. In this disease, which is apparently a newcomer to the pathological scene in Britain, fibrino-purulent exudate is found also in the serous cavities.

In erysipelas and more particularly in salmonellosis, a serous meningitis and low grade vasculitis may be found. The process is not usually frankly purulent but odd polymorphs may be seen in the exudate especially in the depths of the cerebellar sulci.

It appears doubtful whether *Leptospira pomona* infection is important as a nervous disease of pigs (Fankhauser & Wyler, 1953) and its principal interest appears to lie in its transmissibility to man. The organism is not known to occur in Britain.

(b) *Local Supperative Lesions*

Listerella (*L. monocytogenes*) although known to be present in the country has not so far been recorded as a cause of nervous disease of pigs in Britain. In contrast to the diffuse meningitis which it produces in sheep, the lesions of listerellosis in the pig are abscess-like and usually involve the medulla oblongata (Biester & Schwarte, 1940; Helmboldt, Jacobs & Case, 1951; Helmboldt & Jungherr, 1952).

Whereas listerellosis involves the brain by haematogenous dissemination, many local bacterial infections are the result of secondary extension from lesions of the bones and intervertebral discs. Osteitis and splondylitis due to tuberculosis or *Brucella suis* infection may extend into the brain or cord and abscesses of the pons and cerebellar peduncles are frequent sequels to middle-ear disease, the organisms most commonly found being *Corynebacterium pyogenes* and *Pasteurella multocida*. Destruction of tissue at the site of these abscesses is usually complete and there are frequently localising clinical signs present.

Tuberculosis

Although Anthony (1954) affirms that tuberculous meningitis is the commonest form of bacterial meningitis in the pig, the author has not yet encountered a single case and it would appear that tuberculosis in the pig is much less common of recent years.

Fankhauser and Wyler (1953) after Joest (1937) distinguished four forms:—

(1) Tuberculosis of the occipital and temporal bones with compression of the adjacent brain, though the dura mater may not be involved.

(2) Pachymeningitis tuberculosa externa in which tumour-like caseous masses project into the cranial cavity in the temporal region causing compression.

(3) Tuberculous leptomeningitis, with typical tubercles consisting of lymphocytes, plasma cells, epithelioid and giant cells sometimes round a caseous core and with periarteritis and endarteritis. The granulomatous process may be confined to the pia or may spread into the C.N.S. proper following the track of blood vessels.

(4) True tuberculous encephalitis and myelitis following haematogenous dissemination, with tuberculomae in the substance of the brain and cord.

Degenerative Lesions

(1) Lesions Characterised by Malacia

Apart from malacic lesions resulting from infarcts (which seem to be most common in the mid brain) and severe local trauma such as that induced by fracture of a vertebra (Hindmarsh, 1935) there appear to be several fairly distinct conditions in the pig.

(a) *Meningoencephalitis eosinophilica*. This condition is characterised by oedema and neuronal degeneration in the cerebral cortex accompanied by vascular proliferation and heavy cellular infiltration (chiefly perivascular) by eosinophiles (see Done, Brooksbank & Buntain, 1957, for references). Though Michalka (1942b) and Hjärre and Obel (1956) describe lesions in the C.N.S. elsewhere than in the cerebrum, we have seen only one case of eosinophilic cerebellar leptomeningitis and the writer is not convinced that these cases are necessarily part of the same syndrome since they do not appear in the experimental disease (Done, Harding & Lloyd). The lesions are most marked in the depths of the cerebral sulci but vascular cuffing in the underlying corpus medullare and eosinophilic leptomeningitis may also be present.

The condition can be reproduced at will by feeding excess sodium chloride and restricting water (Smith, 1955; Hjärre & Obel, 1956) but whereas these workers considered that the Na ion is primarily involved, work at Weybridge (Done, Harding & Lloyd) suggests that a non-specific disturbance of the water balance is responsible for the initial cortical oedema and necrosis and that the spectacular eosinophile activity is a reflection of the high sodium concentration in the blood.

Confirmation of the complicity of excess sodium chloride in cases of meningoencephalitis eosinophilica may be obtained by chloride estimation on the cerebrum. Bohosiewicz (1954) quotes 0.14 to 0.18 per cent. Cl as normal levels with values in excess of 0.18 as suspicious of salt poisoning.

(b) *Polioencephalomalacia (Hartley)*. Recently Hartley (1957) in a personal communication described 3 cases of a symmetrical cortical necrosis in young pigs apparently similar to the polioencephalomalacia of cattle and sheep recorded by Jensen, Grimer and Adams (1956). The malacic lesions which show no signs of sepsis and contain large numbers of gitter cells differ from those of meningoencephalitis eosinophilica in their location just under the surface of the brain, in the completeness of necrosis, lack of vascular proliferation and absence of eosinophile infiltration, but may possibly reflect a similar metabolic derangement.

(c) *Cerebrospinal Nematodiasis*. It is customary in text-books on veterinary parasitology to suggest that nervous signs observed in outbreaks of porcine ascariasis are produced by the presence of aberrant larvae in the C.N.S. but there is as yet little support for this belief in fact.

Although Sprent (1955) recorded finding two *Ascaris suum* larvae in the brain of one of 5 pigs suffering from posterior paralysis he gave no account of the histopathology of the C.N.S. in this case and it is possible that the presence of the larvae was unconnected with the clinical disease since Done, Gibson and Harding (1956) were unable to induce nervous signs, or to demonstrate lesions in the brain following the introduction of *A. suum* larvae into either the systemic circulation or directly into the cerebrum. Sprent was unable to induce cerebrospinal nematodiasis in one pig after oral dosing with eggs of *A. suum*.

On the other hand, Done, Windsor and Gibson have obtained counts of up to 28 larvae per gramme in pig brain 8 days after oral dosing with embryonated eggs of *Toxocara canis*. This accords with observations on visceral larva migrans in children (Beautyman & Woolf, 1951; Dent, Nichols, Beaver, Carrera & Staggers, 1956) and illustrates the theory (Sprent, 1954) that larvae of a species having a somatic type of migration (like *T. canis*) are much more likely to be found in the C.N.S. than those of a species migrating *via* the trachea (like *A. suum*).

To date no pathological description of a case of cerebrospinal nematodiasis in the pig has been published but the author has seen 2 cases in which damage to the lumbar cord was similar to that described in goats (see Innes & Shoho, 1952). In one case there were several malacic tracks traceable for some distance along the cord though no larvae were positively identified in the sections. There was some endothelial swelling and mild vascular infiltration around the malacic zones which did not follow any obvious anatomical arrangement, but in the damaged areas cellular infiltration was confined to a few leucocytes. In the meninges there was local perivascular infiltration by round cells.

(d) *Local Myelomalacia*. Fankhauser and Wyler (1953) have described a case of local poliomyelomalacia in the lumbar cord following spinal anaesthesia and the author has seen what appears to be a similar lesion also in the lumbar cord but no history of surgical interference was given. The lesion was fusiform, yellowish grey in colour and occupied the area bounded by the dorsal horns and the central canal. It consisted of necrotic nervous tissue with some attempt at granulation and was surrounded by a zone of astroglial proliferation.

(2) Lesions Characterised by Demyelination without Malacia

(a) *Enzootic Ataxia*. Since 1952 a condition provisionally named enzootic ataxia of swine has been recognised in Britain characterised by demyelination in the dorsal bundles of the cord and to a lesser ex-

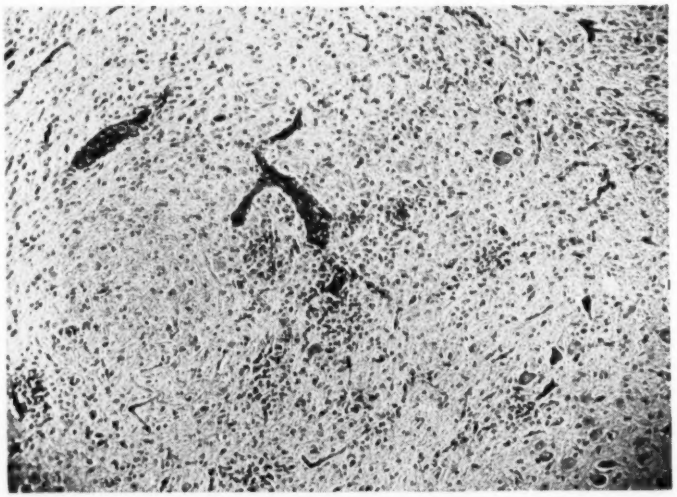

FIG. 1.—Swine fever. PD2227. Medulla oblongata. H. & E. x 80. Showing vascular cuffing and focal microglial infiltration dorso-lateral to the calamus.

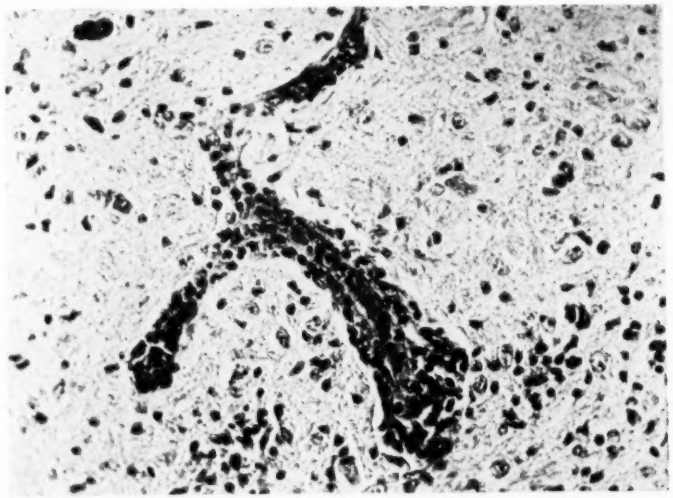

FIG. 2.—Swine fever. Detail of Fig. 1. x 270. The vascular endothelium is swollen and the blood vessel wall and perivascular space are infiltrated by round cells.

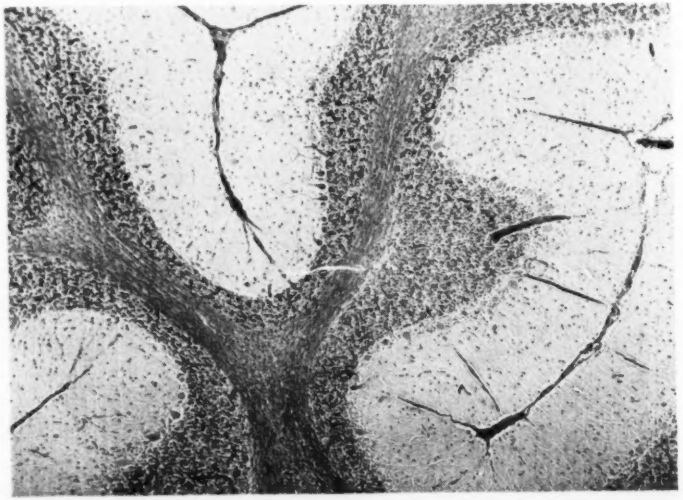

FIG. 3.—Swine fever. PD2227. Cerebellum. H. & E. x 50. Compared with the other virus encephalomyelitides the cerebellum is little affected in swine fever. There is some vascular cuffing and local round cell infiltration of the leptomeninges.

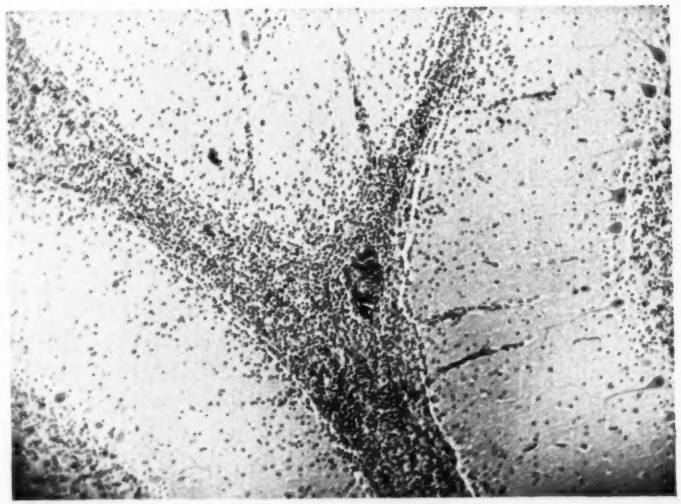

FIG. 4.—Suppurative leptomeningitis. PD3428. Cerebellum. H. & E. x 80. The interfoliar clefts are distended with purulent exudate which is spreading into the molecular layer of the cerebellar cortex.

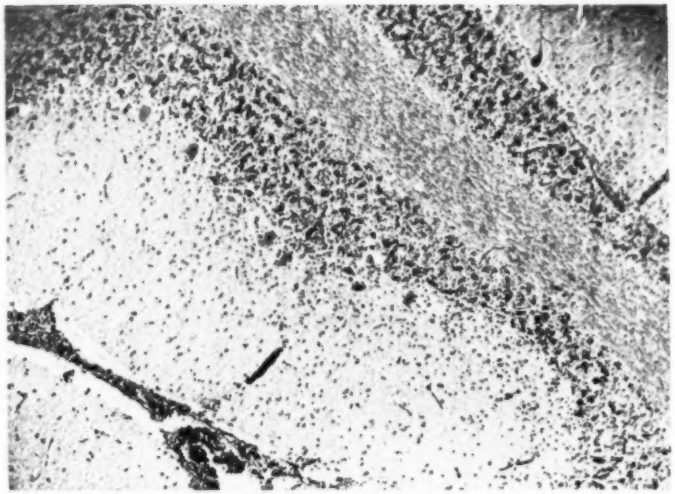

FIG. 5.—Louping-ill. PD255. Cerebellum. H. & E. x 80. Damage is most severe in the cortex where many of the Purkinje cells are surrounded by phagocytes. There is also a non-suppurative leptomeningitis.

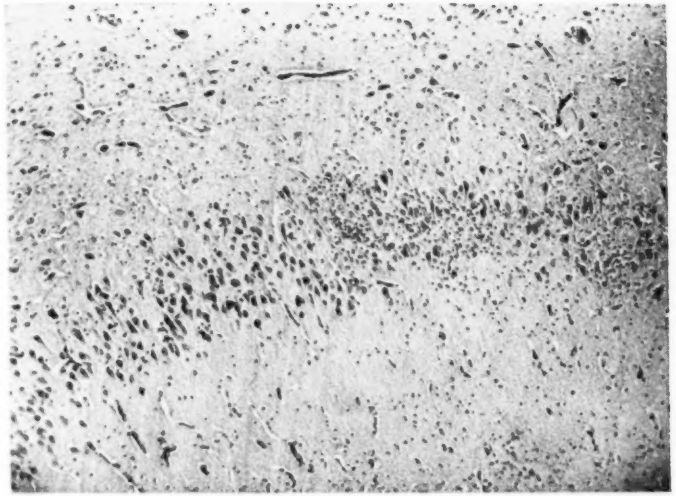

FIG. 6.—Aujeszky's Disease. PD553. Cerebrum. H. & E. x 80. Motor cortex, showing localisation of the cellular reaction in the large neurone layer.

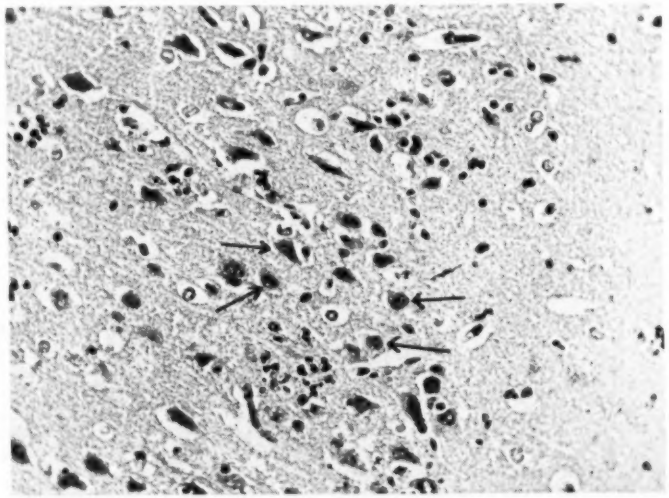

FIG. 7.—Aujeszky's disease. PD553. Cerebrum. H. & E. x 270. The deeply staining neuronal nuclei are full of material staining slate blue to purple, while a number of others (shown by arrows) contain one or more inclusions.

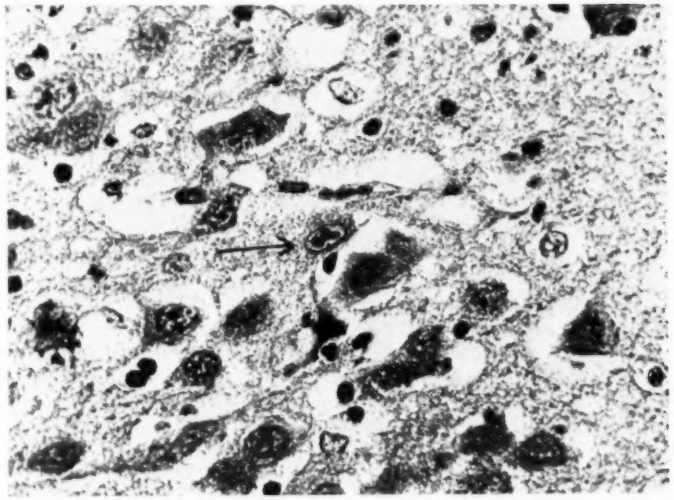

FIG. 8.—Aujeszky's disease. PD553. Cerebrum. H. & E. x 575. In the centre of the field is a cell with a thickened nuclear membrane and prominent intranuclear inclusion. Below it a neurone is undergoing neuronophagia.

inclusions.

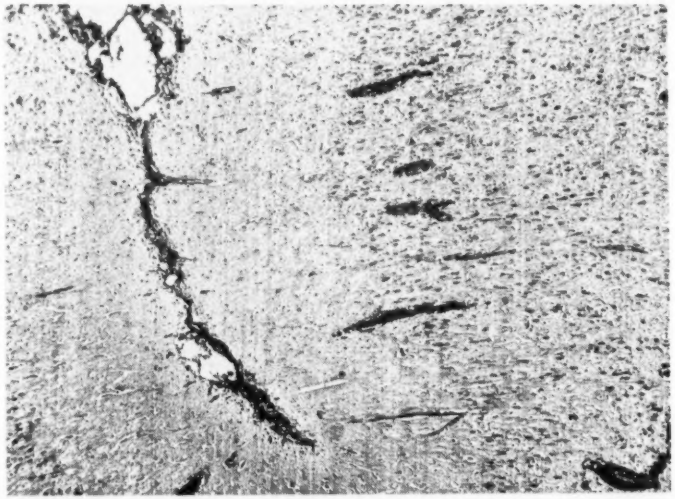

FIG. 9.—Meningoencephalitis eosinophilica. PD176. Cerebrum. H. & E. x 50. There is a zone of hydropic degeneration and vascular cuffing around the sulcus and eosinophile infiltration of the leptomeninges.

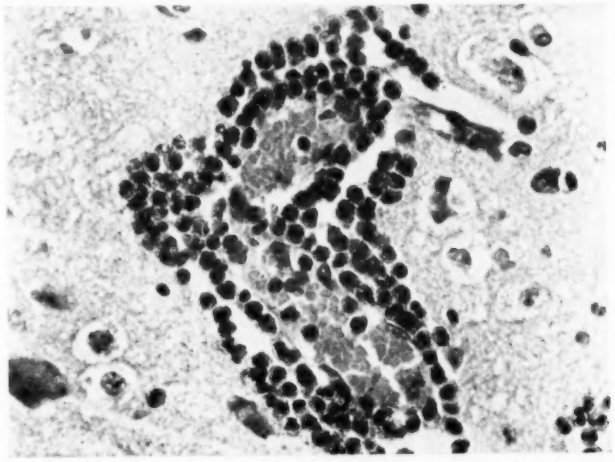

FIG. 10.—Meningoencephalitis eosinophilica. PD176. Cerebrum. H. & E. x 575. Detail of a cuffed vessel. Almost all the infiltrating cells are eosinophiles.

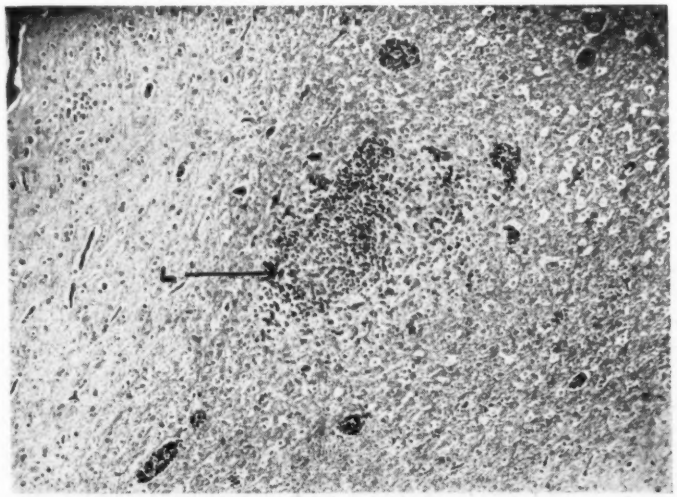

FIG 11.—*Visceral larva migrans*. PD3308. Cerebrum. H. & E. x 80. Granulomatous reaction and perivascular cuffing characteristic of the later stage of the disease, with a *Toxocara canis* larva (L) cut obliquely.

FIG. 12.—*Visceral larva migrans*. PD3118. Anterior corpora quadrigemina. P.A.S. x 270. *Toxocara canis* larva in the brain 8 days after experimental infection. At this stage active migration of even large numbers of larvae produces little or no reaction in the C.N.S.

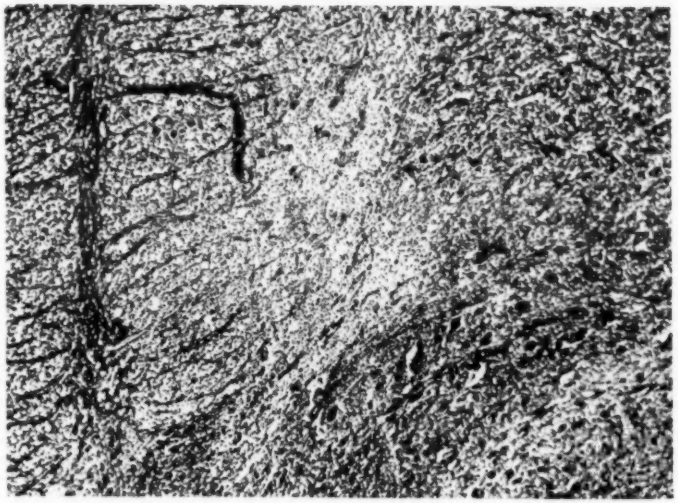

FIG. 13.—Infarct. PD3309. Medulla. Masson's trichrome. x 50. The malacic area contains large numbers of foam cells. There are some swollen axon cylinders dorso-medial to the lesion.

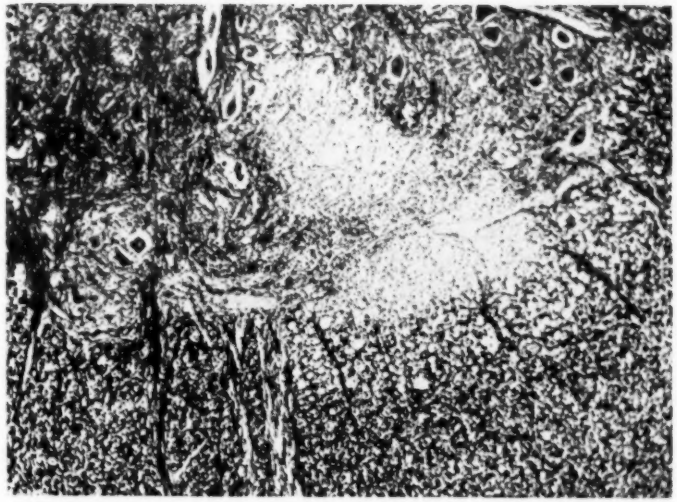

FIG. 14.—Spinal malacia. PD1468. Lumbar cord. Copper phthallocyanin. x 50. Malacic lesion at the ventral border of a motor horn. The lesion pursued a tortuous course along the cord and suggested the passage of a metazoal parasite.

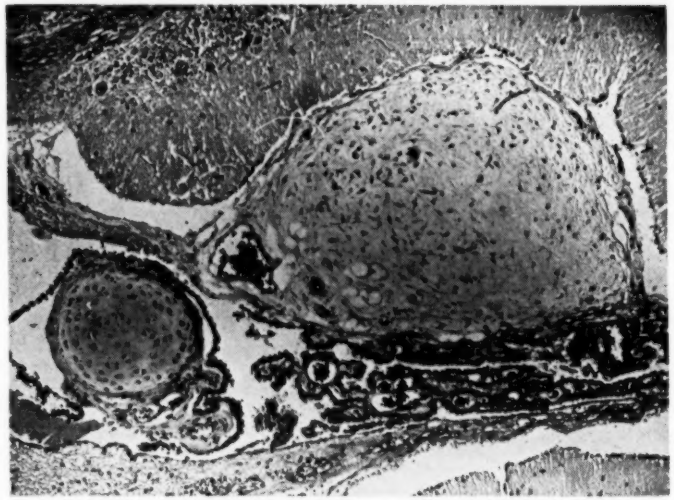

FIG. 15.—Neoplasia. PD3234. A small tumour containing fat, cartilage and myxomatous elements and lying in the fourth ventricle. H. & E. x 80.

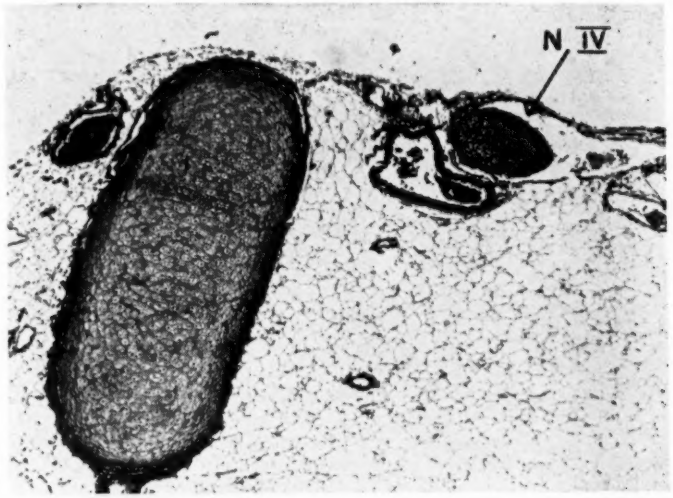

FIG. 16.—Neoplasia. PD3069. Part of a lipoma containing cartilage which lay above and behind the corpora quadrigemina. The trochlear nerve lay on the upper surface of the tumour. Masson's trichrome. x 50.

tent also in the cerebellar folia. It was formerly regarded as being possibly familial, but it now seems that it may well have been the chronic stage of Tartan disease *q.v.*

(b) *Neonatal Spinal Demyelination.* McClymont (1954) has described an outbreak of disease in which 6 sows produced complete litters of piglets paretic at birth. Pathologically there was myelin degeneration in the ventral and ventro-lateral bundles in the spinal cord though the dorsal funiculi were normal. No cause was identified.

(c) *Nutritional Deficiency.* Of the degenerative nervous lesions in pigs ascribed to vitamin deficiencies only that due to deprivation of pyridoxine and pantothenic acid seems to be reasonably well substantiated from the pathological point of view. (Wintrobe, Mitchell & Kolb, 1938; Wintrobe, Miller, Follis & Stein, 1942; Swank & Adams, 1948). An ascending degeneration of the peripheral nerves, dorsal root-ganglia and dorsal columns of the cord is described.

(d) *Toxic Conditions.* The writer has seen widespread perivascular demyelination in a sow with a septic metritis which had been recumbent for over a week and comatose for several days before death and it is presumed that other toxic conditions may cause this type of lesion.

The organo-phosphorus compounds paralyse by inhibiting cholinesterase and produce demyelination. The author has seen only one case of experimental poisoning by Mipafox but would hesitate to place much diagnostic reliance on the relatively little demyelination which was visible in the brain and cord.

Mechanical Effects

The transverse myelitis resulting from a fractured vertebra has already been mentioned, and according to Hutyra, Marek and Manninger (1951) a similar lesion may follow displacement of an intervertebral disc. Durréchoux (quoted by Hutyra *et al.*, 1951) observed a case of a needle in the cerebellum of a pig but such accidents must be extremely rare.

Although as Dorothy Russell (1949) has pointed out in her excellent monograph, the usual text-book headings of "congenital" and "acquired" under which hydrocephalus is discussed are virtually meaningless in the light of morbid anatomy, they constitute a classification intelligible to the clinician and it must be admitted that so little is known of the pathogenesis of hydrocephalus of the pig that a purely pathological classification does not yet seem possible.

Some degree of "acquired" hydrocephalus usually develops in the bacterial meningitides of the pig especially in streptococcal chloriomeningitis but there is a further form from which inflammatory involvement of the cisterna magna is absent and which is believed to result from a hypovitaminosis A. In this form there is herniation of the posterior lobe of the cerebellar vermis through the foramen magnum and multiple haemorrhages in the molecular layer of the cortex of the herniated part. Histologically cellular infiltration of the meninges is absent and the only lesions seen are cortical haemorrhages and axonal degeneration in the cerebellum, usually affecting only the most posterior part of the vermis.

Arachnoiditis (chronic leptomeningitis) is also a frequent sequel to tuberculous and purulent leptomeningitis and may be expected to increase in incidence following widespread use of antibiotics to treat animals which would formerly have died in the acute stage of the disease. The presence of arachnoiditis is usually associated with disease of the blood vessels since the leptomeninges themselves behave as if they were non-reactive neuroglial tissue supporting vulnerable vascular tissue with a highly reactive adventitia.

Neoplasms of the C.N.S. of the pig appear to be fairly rare and those actually producing nervous damage rarer still, *vide infra.* There are probably rather more instances in which tumours of non-nervous tissues are responsible for pressure damage. De Gruchy (1956) brought to our notice a case in which a rapidly growing mixed sarcoma of a thoracic vertebra was responsible for posterior paralysis in a five-week-old pig.

Of tapeworm cysts, *Cysticercus cellulosae* is said to occur in pigs' brains with some frequency by Joest (1937) though Fankhauser and Wyler (1953) have not seen it, nor have we. Glasser, Hupka and Wetzel (1950) say that *Coenurus cerebralis* has only once been recorded in pigs.

Vascular Accidents and Disease

Haemorrhages are frequently encountered as artefacts in brains removed from the pig soon after death as often occurs when the animal is killed for examination, but there are several types of true haemorrhagic lesion to interest the pathologist.

The cerebellar cortical haemorrhages of hypovitaminosis A have already been referred to but a lesion similar in appearance though widespread throughout the brain may occur in purpuric states. Arteriolar haemorrhage associated with fibrinoid degeneration of the media of the type described by Obel (1953) in hepatosis dietetica has also been seen in the brain.

As has already been said, arachnoiditis is a fairly frequent finding and endarteritis and periarteritis are commonly associated with it. A plexiform reduplication of the median spinal artery has also been seen by us in one instance, and anterioslerotic lesions in the brain are relatively common considering the comparative youth of many of our subjects. Infarction without thrombosis is at least as common as with thrombosis, and probably results in many cases from arterial spasm following chronic vascular disease.

Neoplasia

Cotchin (1956) in his review of the neoplasms of the domesticated animals makes no mention of neoplasms of the C.N.S. of the pig and indeed there appears to be only one previous report, that of Schönberg (1926) of a "lipoma durum" between the cerebral hemispheres in an 8-month-old pig.

At Weybridge we have encountered 3 cases of lipoma and one of a lipochondromyxoma in the fourth ventricle, a pedunculated lipoma containing cartilage lying on the left side of the brain between the origin of the fourth cranial nerve and the corpora

quadrigemina and a case with metastatic lymphoblastic nodules in the choroid plexuses, but the only neural tumour of which we have heard is a glioma occupying a considerable part of the left cerebrum of a 4-month-old Large White pig (Gellatly, 1953).

Developmental Abnormalities

It is usual to attempt to divide developmental abnormalities rigidly into hereditable and non-hereditable types, but the author feels that in the present state of our knowledge this has little to commend it since recent work suggests that at least some abnormalities, *e.g.*, the microphthalmia/anophthalmia syndrome may be the result either of heredity, nutrition or maternal infection during early pregnancy, or possibly some combination of these. The situation is complicated by the fact that the pathological characters of many of the allegedly hereditable nervous disorders have not been adequately described, if at all, but a check list of such conditions is provided by Saunders (1954).

Of the developmental abnormalities affecting the C.N.S. some are incompatible with the survival of the animal *per se* (as meningocoele or meningoencephalocoele) or because they are part of a more extensive deformity (as in conjoined monsters or cyclopic piglets) but there are others, the existence of which is either not suspected or which appear to affect the piglet only to a limited extent, though they may be the source of overt clinical disease later in life or complicate the pathological picture in cases of intercurrent nervous disease (see Fankhauser & Wyler, 1953, for review of literature).

Hydrocephalus and also meningocoele are not uncommon in the new-born pig though little is known of their pathogenesis. The interested reader is referred to Russell (1949) for a consideration of possible mechanisms.

In this country the anophthalmia/microphthalmia/macrophthalmia syndrome is fairly common and in a surprisingly large percentage of cases the condition is not noticed until the pigs are several weeks, or even months, old. (Hale, 1937; Bendixen, 1944; Roberts, 1948; Maneely, 1951; Hubrig, 1954; Watt & Barlow, 1956; Harding & Done, 1956.)

According to Schulz (1953) local cerebellar cortical aplasia occurs in most pigs and he also observed generalised hypoplasia of the cerebellum in 2 pigs. The present author has encountered one case of gross undersize of the whole brain associated with ataxia.

Seibold and Roberts (1957) have described a syndrome in young pigs consisting of inco-ordination, ataxia, dizziness, unthriftiness and finally death which they believe to be associated with misshapen nuclei in some of the Purkinje cells of the cerebellum. They believe the condition to be congenital anomaly.

According to recent work by Christensen and Christensen (1956) "trembling" in new-born piglets is a functional disorder associated with the delayed myelination, especially of the spino cerebellar tracts, but in view of the considerable variation in the state of myelination in the normal new-born pig, it is not the present author's experience that one can differentiate affected from non-affected piglets with any confidence on this basis.

Pigmentation of the brain and meninges is common, indeed usual in the black breeds of pigs, especially the Essex and Wessex, and the amount of pigmentation which may be found in the lateral lobes of the cerebellum, especially at the junction of the granular and molecular layers is sometimes spectacular. Turbes, Richards and Abreu (1956) have commented on the presence of the pigment in piglets showing tremors of unknown aetiology but the present author has been unable to find any constant association with clinical disease in his series and it is perhaps worth noting that in many cases of trembling disease in piglets, pigmentation of the brain has been completely absent.

Diastematomyelia has been seen by the writer in the lumbar cords of 3 pigs, and in each case the condition appeared to cause the animal no inconvenience. It has also been reported by Holz (1956).

Diseases With no Known Lesions

There are a number of nervous conditions in which no constant and characteristic organic lesions have been observed. This may be because either there are none to be seen or because suitable techniques for their demonstration are not available, or because the pathologist is insufficiently familiar with the normal, though this latter factor has probably more often led to the ascription of pathological significance to perfectly normal structures. In this respect, attention is called to the observation of Lindenberg (1956) that contrary to expectation sudden death produces more pronounced "*post-mortem* degeneration" than prolonged anoxia preceding death.

In some cases the lack of knowledge of the neuropathology of even familiar clinical entities was simply due to the fact that no one had examined the appropriate organs, as was the case until very recently with salt poisoning. Poisoning by arsenilic acid (Oliver & Roe, 1957) and other agents probably fall into this group.

Of diseases associated with bacterial toxins, tetanus, botulism and oedema disease are three examples of conditions with definite nervous involvement, but without demonstrable organic lesions of the C.N.S. It is interesting to speculate whether the toxin used by Erskine, Sojka and Lloyd (1957) to produce experimental oedema disease contains a specific neurotoxin or whether it acts purely on the vascular system as has been demonstrated for Shigella neurotoxin (Cavanagh, Howard & Whitby, 1956). The present author does not regard the changes in the cerebrum described by Köhler (1951) as significant in relation to oedema disease.

In piglets with congenital paralysis, as seen in this country, the pathological basis for the clinical picture could not be determined on material examined by routine methods and clearly this is one of the conditions which needs more detailed study.

It seems probable that idiopathic epilepsy occurs in pigs, cases having come to the writer's notice of pigs which manifested epileptiform seizures, though no sign of organic disease could be found at autopsy.

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THE SPEAKER'S INTRODUCTION

Mr. Done commenced by thanking his colleagues in the Investigation Service of the Ministry of Agriculture, Fisheries and Food for providing the bulk of the material

on which his work was based. This was essentially a co-operative effort between the man in the field and the man at the microscope.

He thought that most of his listeners who had had a good deal to do with pigs would agree that they were not yet able to recognise more than a small proportion of the diseases from which the pig suffered and that it was unlikely that they would be able with confidence to diagnose clinically conditions which had not yet been defined and differentiated pathologically.

In the last 50 years research into pig diseases in this country and in America had been chiefly of an inductive rather than a deductive type, with the result that, while the aetiologists (bacteriologists, parasitologists, etc.) had flourished, both clinical and pathological arts had decayed and differential diagnosis had often degenerated into wishful thinking or sheer empiricism.

He believed that the most useful first step in the study of a disease in an animal was the pathological differentiation of all the diseases affecting the organs in question in the species concerned. Once that was reasonably well established, differentiation on an aetiological and clinical basis followed on naturally.

Mr. Done said that his paper was an attempt to provide in skeleton form, at the risk of possible over-simplification, a working guide to the known or suspected diseases of the central nervous system in the pig. On reading the paper through again, he thought it was the driest composition that he had encountered for some time, though he thought that this was due in part to the fact that it consisted very largely of bare bones, and he looked forward to hearing them clothed with the meat of experience.

The author referred to three problems which had been receiving attention since the paper was written. First, with reference to the group of virus polioencephalomyelitides, recent work by Chaproniere, Done and Andrewes using tissue cultures had shown that viruses of Talfan disease, Teschen disease and poliomyelitis suum cross-neutralise, and furthermore that after two passes in tissue culture Talfan virus can assume a virulence equal to that attributed to Teschen virus.

Secondly, further work on experimental visceral larva migrans in the pig by Done, Windsor and Gibson, using *Toxocara canis* had shown that not only would *Toxocara canis* larvae migrate through the central nervous system in considerable numbers but that they could provoke a reaction which resulted in organic and clinical disease. Thus, considering the gastronomic habits of the pig, naturally occurring cerebrospinal nematodiasis must be considered as a possibility, though a rare one.

Thirdly, it was stressed that vascular disease appeared to be far from rare in the pig, especially in view of the early age at which the majority of pigs were killed, and that this was as true of the central nervous system as of other organs. Infarction unassociated with thrombosis was relatively frequent and lesions suggestive of hypertension could be found in pigs of two to three months of age, and sometimes younger.

The address concluded with a display of slides showing gross and microscopic lesions of the central nervous system.

The Opener

Mr. J. B. M. Gellatly, said: "It is both an honour and a pleasure to open the discussion of Mr. Done's paper, not only because of its high intrinsic value to the laboratory worker engaged in routine diagnosis, but also because it fills a large gap in British veterinary literature. It is perhaps not widely appreciated that whereas there are several text-books of veterinary neurology and neuropathology in German, some devoted exclusively to one species, there is in English only one such book and this is concerned solely with canine nervous disease. Moreover, the accuracy of diagnosis of any disease in any country is frequently a reflection of the quality of that country's literature; thus the paucity of our knowledge of nervous disease in the pig has, until recently, merely paralleled the almost complete absence of this subject from British veterinary publications. It is only against this background that the true value of Mr. Done's paper can be fully appreciated.

"In his paper Mr. Done has stressed the frequency of occurrence and the variation in aetiology of porcine nervous disease. I should like to select for discussion certain aspects, some purely academic, some of considerable economic importance.

Congenital Abnormalities and Neoplasia

"Mr. Done has listed a series of congenital abnormalities of the nervous system, many of which are recognised during routine autopsies. To these I should like to add two more. We have encountered two cases of absence of the corpus callosum in Large White piglets aged 6 to 13 days old. This lesion which was unassociated with any clinical signs is well recognised in human neuropathology and has already been described by Schellenberg (1909) in a pig. We have also recognised one case of the Arnold Chiari malformation in a new-born male Large White piglet. This abnormality is comparatively rare in man and, to my knowledge, has not previously been reported in veterinary literature. The Arnold Chiari malformation is recognised by the presence of a tongue-like prolongation of the cerebellum which protrudes through the foramen magnum, overlapping an elongated medulla oblongata. In our case it was associated with a well defined lumbar spina bifida of meningomyelocele type and may possibly have been produced by posterior meningeal traction during the development of this malformation of the spinal column. Death was due to a secondary hydrocephalus. Within recent years our knowledge of the aetiology of congenital malformations has expanded considerably, the most notable contribution being the recognition of the influence of intercurrent maternal infection during pregnancy. I feel, however, that we must avoid exploiting this attractive hypothesis.

"In dealing with neural tumours Mr. Done has mentioned a glioma which we have encountered in a 4-month-old Large White boar. This tumour was roughly oval in shape, 3.5 x 3 cm. in size, and occupied approximately 70 per cent. of the left cerebral hemisphere. Histologically, the tumour appears to be a very poorly differentiated glioma and shows evidence of growth by expansion and infiltration. Clinically, a middle ear infection was initially suspected but later the animal showed evidence of paraplegia and blindness of insidious onset and development.

Leptomeningitis, Arthritis and Serositis

"In his paper, Mr. Done has described this group of diseases under the heading 'Diffuse Suppurative Meningoencephalitis and Myelitis.' In our experience in Edinburgh this group is one of the most important causes of mortality in pigs under 60 days of age (see Table I). Thus, if losses from stillbirths, crushing, starvation, etc., in the immediate post-natal period are excluded, over 18 per cent. of all deaths in the age group 6 to 60 days are attributable to this syndrome.

TABLE I.

INCIDENCE OF LEPTOMENINGITIS, ARTHRITIS AND SEROSITIS, 1952-7.

Age in Days	Number Examined	Number Affected	% Affected
0 - 6	3,365	6	0.18
6 - 60	928	169	18.21

"While in his paper Mr. Done has differentiated between streptococcal choriomeningitis and arthritis on the one hand, and Glasser's syndrome of serositis and arthritis on the other, our findings indicate that Streptococci produce a fibrinous serositis in approximately 50 per cent. of cases showing arthritis and choriomeningitis (see Table II). I feel, threfore, that the differentiation between streptococcal choriomeningitis and arthritis and Glasser's syndrome is not fully justified, on the grounds that both entities have a similar pathogenesis and that the reaction produced is independent of the causal agent.

TABLE II.
SITE INCIDENCE—175 CASES

Joints	Leptomeninges	Pleura	Peritoneum
145	95	67	47
82.9%	54.3%	38.3%	26.9%

"It is perhaps not fully appreciated, however, that although the incidence of leptomeningitis, arthritis and serositis is highest during the second, third and fourth weeks of life (see Table III) cases may be recognised at any time between 2 days and 3 months of age. We have found, for instance, that between 50 and 60 days there is, particularly in male pigs, a sharp rise in the incidence which may be attributable to infection of castration wounds.

TABLE III.
AGE INCIDENCE 0-60 DAYS

Age in Days	Number of Cases	% Incidence
0 - 5	8	4.6
5 - 10	16	9.1
10 - 15	29	16.6
15 - 20	29	16.6
20 - 25	27	15.4
25 - 30	17	9.8
30 - 35	17	9.8
35 - 40	13	7.4
40 - 45	2	1.1
45 - 50	2	1.1
50 - 55	6	3.4
55 - 60	9	5.1

"Bacteriological examination of 146 of the 175 cases which we have recognised since January 1st, 1952, has been carried out by my colleagues in the Department of Veterinary Bacteriology and their findings show that Streptococci were isolated from 116 (79.5 per cent.) of these cases, of which 61 (41.9 per cent.) were alpha haemolytic (see Table IV). Although the incidence of Coli group infection has been comparatively low, all 5 cases which we have encountered have been recognised during the past 7 months. Since such Coli group infections may readily be differentiated on a histological basis by the enormous number of organisms present in the leptomeninges and synovial villi, and since these organisms are not susceptible to penicillin therapy, the significance of this infection may require careful review in the near future. In Guelph, Gwatkin and his colleagues have stressed the importance of P.P.L.O. in this syndrome but I feel that the consistency with which Streptococci are isolated in Britain suggests that P.P.L.O. may play little part in the pathogenesis of leptomeningitis, arthritis and serositis in this country.

TABLE IV.
BACTERIOLOGICAL FINDINGS—146 CASES.

α-Haemolytic Streptococci	61	(41.9%)
β-Haemolytic Streptococci	39	(26.7%)
Non Haemolytic Streptococci	16	(10.9%)
All Streptococci	116	(79.5%)
Coli Group	5	(3.4%)
Miscellaneous	25	(17.1%)

Virus Infections of the Central Nervous System

"Without doubt the *pièce de résistance* of Mr. Done's paper has been the information which he has given us concerning Talfan disease. My own experience of this disease is comparatively limited but the similarity of the lesions in the dorsal root ganglia to those of herpes zoster in man is in some cases quite striking. I should be very interested to hear Mr. Done's views on the possible methods of spread of this disease. particularly when one bears in mind the frequency with which other virus infections of the central nervous system in domesticated animals are transmitted by ectoparasites, since in at least one of our suspected cases of Talfan disease heavy lice infestation was present.

"While Mr. Done's information on Talfan disease will be welcomed by laboratory workers throughout the country I feel that the most important part of his paper concerns the neuropathological diagnosis of swine fever. For over 20 years it has been recognised that lesions occur in the central nervous system in a high proportion of cases of swine fever. During this period a number of workers have suggested that the lesions which develop are not of sufficient specificity to warrant their utilisation as an aid to diagnosis. This has not been my experience in Edinburgh where histological examination of the pons and medulla in particular has proved during the past 5 years of great value in differential diagnosis. One major objection to the use of neurohistopathology as a diagnostic tool has been the existence of other unidentified virus infections of the central nervous system of the pig. In recent years, however, the work of Done and his colleagues on Aujeszky, louping-ill and Talfan disease in particular has shown conclusively that the nervous lesions in swine fever can be differentiated histologically from all other virus diseases of the central nervous system at present recognised in Britain.

"It is my opinion that those who belittle this aid to diagnosis have themselves failed to appreciate the fundamental pathogenesis of swine fever; moreover, I consider that the time has now come for a critical re-appraisal of the methods at present in use in Britain for confirmatory diagnosis of this condition. We must appreciate that the causal agent of the disease has a marked affinity for vasculo-endothelium and that while in the central nervous system a pure virus reaction is preserved uncomplicated by secondary bacterial infection, the classical 'button ulcers' depend for their formation on the combination of primary virus activity and secondary intestinal bacterial infection. As a result such ulcers seldom appear until comparatively late in the disease. Yet, in the interim, vasculo-endothelial degeneration and proliferation, perivascular mononuclear cuffing and gliosis may be readily appreciated in the central nervous system, while evidence of vascular damage, such as haemorrhage, infarction and necrosis, may be recognised in lymph nodes, spleen, kidneys, alimentary tract, etc. It should be stressed, however, that the diagnosis of swine fever in very young pigs up to 10 days of age remains a problem, since such animals frequently appear to die during the initial viraemia before appreciable vascular damage has been produced.

"On this basis and until other reliable diagnostic procedures are available, I consider that histological examination of the central nervous system is an important ancillary aid to diagnosis which, with haemotological and bacteriological examinations, should be more frequently utilised to augment the epizootiological and clinical investigation of swine fever.

Laminar Cerebral Cortical Necrosis

"During the past 2 years we have recognised in pigs under 2 months of age a syndrome characterised clinically by depression, circling and opisthotonus, and pathologically by laminar cerebral cortical necrosis. In most of our cases the syndrome has been associated with dehydration secondary to scouring or reduced water intake and anoxia due to extensive pneumonia. The syndrome has affected only one or two pigs in any one litter. Macroscopically a thin yellow band may be recognised in the inner cortex at all levels of the cerebrum while on histological examination a zone of necrosis can be appreciated in the middle layers of the cortex with almost complete integrity of the deepest layers adjacent to the white matter. The necrosis appears to be of vascular origin since the cortical arterioles and capillaries show pronounced thickening of their walls and partial luminar occlusion. Although some increase of mesenchymal cellularity may be appreciated, this is mainly a reactive gliosis with mild macrophage/lymphocyte infiltration. In one case, however, a pronounced leptomeningitis eosinophilica was recognised. This syndrome therefore shows certain characteristics of both leptomeningitis eosinophilica and the polio-encephalomalacia encountered by Hartley but it

appears to be even more closely related to that described by Douglas (1949) in a human patient dying of anoxia following thyroidectomy.

"In conclusion I should like to congratulate the Eastern Counties Veterinary Society on their wisdom and foresight in asking Mr. Done to prepare this paper which will, I am sure, for many years remain a standard work of reference for those of us in this field engaged in teaching, research or routine diagnosis. I should also like to take this opportunity of thanking Mr. Done and his colleagues for their many valuable contributions to our knowledge of pig diseases during the past few years and wish them every success in their future investigations."

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The General Discussion

Mr. A. R. Jennings (Cambridge): "I should like to congratulate Mr. Done on his survey of some of the diseases of the central nervous system of the pig and also to thank Mr. Gellatly for his splendid opening of the paper.

"I wish to endorse the remarks of the speakers on the value of histological examinations in cases of swine fever. This method of diagnosis is a very reliable one and it is surprising that it is not used in this country—or perhaps it is? Could the speaker or someone from the Central Laboratory let us know what criteria are used in the diagnosis of swine fever? Histological criteria have been used for many years in Europe and in the U.S.A. and the value of this method of diagnosis is well attested. We use this method in Cambridge and are satisfied that it gives us a rapid and accurate diagnosis. In some outbreaks of the disease we have reported the condition to the appropriate authority but official conformation has frequently taken many weeks during which time the disease has smouldered on and, perhaps, spread well beyond the original focus.

"With regard to the virus encephalitides of swine I am not clear as to the relationship between Teschen, poliomyelitis serum and Talfan disease. We have encountered cases of porcine encephalitis in East Anglia which clinically and histologically were indistinguishable from poliomyelitis suum (Bendixen's paralysis). Has Mr. Done carried out cross immunity tests with these agents? The three diseases bear a very close resemblance to each other—are they, in fact, one and the same disease?

"We have seen a case of what we believe to be cerebrospinal nematodiasis in which there was extensive softening and demyelination of the spinal cord. The parasite was not detected. I have not encountered the vascular lesions described by Mr. Done except for the medial necrosis or fibrinoid degeneration which is seen in cases of liver dystrophy of the type described by Obel.

"With regard to the herniation of part of the cerebellum in pigs affected with avitaminosis A we have not seen this lesion although we examined the C.N.S. most carefully. Did these cases occur in field cases of the disease or was the avitaminosis deliberately induced?

"Has Mr. Done looked for evidence of infection with the virus of lymphocytic chorio-meningitis since this virus parasitises a wide range of animals?"

Professor Lamont (Belfast) said that this was a very important paper and he was delighted that Mr. Done had got all this information together within reasonable compass. The developments in the study of neurological viruses were most interesting. He would like to say that in Northern Ireland they found the examination of sections from the C.N.S. extremely useful in the confirmation of swine fever diagnosis.

Mr. Gellatly later in the general discussion referred to some points which had been raised by Professor Lamont concerning the incidence of arthritis and meningitis. Many of these cases had been found at 7 farms; possibly 60 or 65 per cent. of the pigs which had been autopsied since January, 1952—the number was almost 3,000—had come from 7 farms. Professor Lamont was right in saying that the incidence might not be so high in the remainder of South-East Scotland, but the incidence was nevertheless important.

Mr. Jennings had mentioned a form of polioencephalomyelitis, and a similar condition had been found in pigs coming from East Yorkshire. The lesions were not quite similar to Talfan disease. The pigs were kept overnight in kennels, having been fed on milk beforehand. They were very much improved in the morning, and one pig survived for 3 days. Some showed lesions of the poliomyelitis type of distribution.

Reference had also been made to media necrosis by Mr. Jennings, and Mr. Gellatly said that he had also identified a similar picture.

Dealing with Dr. Campbell's reference to "cuffing" in pigs, he said that he had never experienced this by itself in cases of swine fever. He did not know the significance of "cuffing," although it had been brought to his attention by several of his colleagues.

He had mentioned the importance, in the diagnosis of swine fever, of the examination of the central nervous system. The importance of the central nervous system in such diagnosis lay in the fact that in it one saw the exact response to virus infection alone, with no secondary bacteria infection. In such places as the lungs and the kidneys one always found a secondary bacteria infection which complicated the initial procedure.

The Reply

Mr. Done, in replying to the discussion, said that Mr. Gellatly had been more than kind to him and had done more than justice to the subject. He accepted Mr. Gellatly's contention that the serositis-arthritis-meningitis syndrome had perhaps been over subdivided. He thought that as a clinical and morbid anatomical syndrome, haemophylus infection, streptococcal infection and *Bact. coli* infection could be put together. *Bact. coli* meningitis appeared to be a recent scourge, and his impression was that it was increasing with the practice of early weaning.

On the question of the possibility of transmission of Talfan disease by lice, he had not yet nad a case of contact infection, even though healthy and infected pigs had been kept together for 25 days. A fact of which he was aware was that if the pigs were not already lice-free on arrival, he deloused them, so that perhaps he had ruined his experimental material in this respect

With regard to the absence of inflammatory reaction in the brain of very young pigs, it had already been said that there was evidence of maternal transmission of swine fever in young pigs; lesions were not found in the brains of infected foetuses. It might be that there was a tendency not to react in the early days of life. That was only an impression, but it appeared that pigs which had died of swine fever in the early days of life did not always show the diagnostic lesions in the brain.

Mr. Done then dealt with the question of the relationship between Talfan, Teschen and poliomyelitis suum. Talfan virus was neutralised by sera against Talfan, Teschen and poliomyelitis suum. Teschen was neutralised by Talfan and Teschen; they had not yet tested poliomyelitis suum. (The poliomyelitis suum sera which he had used had been supplied by Dr. Christensen, of Copenhagen.) There was little doubt that these were either the same conditions or indistinguishable variants. Neither Teschen nor Talfan viruses were related immunologically to human poliomyelitis virus of types I, II and III.

In reply to Mr. Jennings's question the cerebellum haemorrhages had been found in field cases of hypovitaminosis A; affected pigs, of store age, had negligible reserves and responded to the administration of vitamin A. With regard to LCM infection, Done & Mansi (unpublished) had been unable to set up disease in pigs even by intracerebral inoculation of the virus, but had encountered one pig with antibodies, suggesting that inapparent infection did occur naturally.

On the subject of "cuffing," he said that the essence of neuropathological diagnosis of swine fever was that this reaction was found in all the principal parts of the brain, and it was not just a collection of odd lesions.

Replying to the question whether pathological changes were common in swine fever, he said that they were found in about 90 per cent. of cases, but it was not an absolute method of diagnosis.

Some Respiratory Diseases of Pigs

BY

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Introduction

RESPIRATORY diseases of pigs are very common, probably because systems of pig management usually provide ample opportunity for the acquisition and spread of various agents affecting the respiratory tract. For example in Great Britain the following incidences of respiratory disease have been reported: Pneumonia 42 to 55 per cent. [2, 6, 62,*] Atrophic rhinitis 10 per cent. [49] and lungworms 13 to 20 per cent. [76, 30].

Respiratory diseases are complicated and confusing because the common diseases are not clearly defined, because different diseases may produce very similar clinical signs and pathological changes and because several agents may affect the animal simultaneously. In many instances there is not enough information available to give a simple description that would make for an easy understanding of these diseases.

Most of the conditions described in this paper have been encountered by the author during field studies of respiratory diseases of pigs. Some of this work was carried out jointly with other workers [12, 96]. Space does not permit description of all the known respiratory diseases of pigs, so only the ones commonly encountered or of particular interest have been selected for description.

Three groups of respiratory diseases are discussed:—

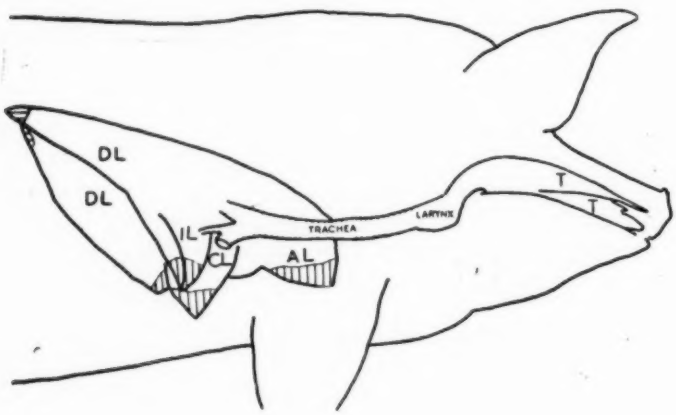
1. Primary respiratory diseases of known aetiology.
   a. Swine influenza.
   b. Lungworm infection.
   c. Aspiration pneumonia.
   d. Acute bacterial pneumonias.

2. Primary respiratory diseases of uncertain aetiology.
   a. Virus pneumonia (Enzootic pneumonia).
   b. Rhinitis.

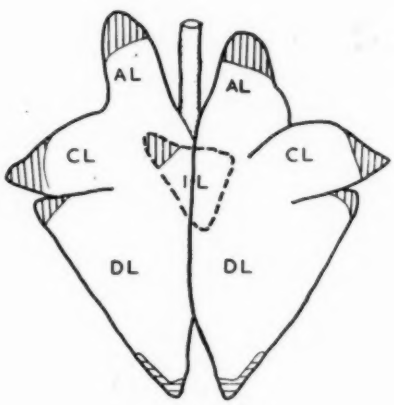
3. Diseases which affect other organs but which also affect the respiratory system.
   a. Swine fever.
   b. *Ascaris lumbricoides* infection.

The accompanying diagrams illustrate the main anatomical features of the respiratory system of the pig.

LATERAL VIEW OF RESPIRATORY SYSTEM



DORSAL VIEW OF LUNG



AL = Apical lobe.
CL = Cardiac lobe.
IL = Intermediate lobe.
DL = Diaphragmatic lobe
T = Turbinate bones

Areas where pneumonia is seen most commonly.

Areas where lungworms usually persist.

*In view of the number of references the names of the authors concerned have been omitted from the text. The small numerals refer to the bibliography at the end of the paper.

1. Primary Respiratory Diseases of Known Aetiology

(a) Swine Influenza

Swine influenza is an acute respiratory disease caused by a virus of the influenza group. *Haemophilus influenza suis* plays an important rôle in the

classical field disease [79]. Influenza virus was isolated from pigs in Ireland in 1938 [54] and in Britain in 1941 [15], but since 1951 no attempts to isolate the virus have been reported. There seems to be no clinical evidence of the occurrence of the classical disease in this country at the present time [6, 97]. The writer has seen experimental cases only. The disease is described because (a) human influenza type A is infective for pigs [42] and so renewed outbreaks of the disease might occur; (b) the disease may occur in the field and not be recognised; (c) the relationship of influenza to other respiratory diseases is still uncertain.

Clinical signs. Human influenza and swine influenza closely resemble each other. Swine influenza occurs mainly in the winter months. The incubation period may be as short as 1 to 2 days, the onset of symptoms being sudden and often the entire herd being characteristically affected within a few days. Clinical signs are severe; there is pyrexia, anorexia, muscular weakness, painful coughing and sneezing. Respirations are rapid and there is a watery discharge from the eyes and nose. Animals lose weight rapidly but in uncomplicated cases rapid and complete clinical recovery occurs in 2 to 6 days. Mortality is low. For further details the reader may consult references [27, 28, 63, 79].

Pathology. Macroscopically there is acute inflammation throughout the respiratory tract with oedema of the lungs and consolidation of the anterior and inferior lobes, [79]. Resolution occurs in a week or two. Microscopically there is alveolar collapse, oedema and exudative bronchitis and there is mononuclear cell infiltration of the perivascular and peribronchial tissues and alveolar walls.

Epidemiology. The rôle of the pig lungworms (*Metastrongylus* spp.) in the perpetuation of swine influenza and the factors responsible for the initiation of outbreaks have been discussed by Shope [79, 80, 81, 82, 83, 84].

Diagnosis. Influenza virus can be isolated from the respiratory tract of pigs only in the acute stages of infection [39, 46]. Recovered animals develop a strong immunity and antibodies can be demonstrated in their sera [38].

(b) Lungworm Infection

The incidence of lungworm infection has been reported by various authors to be 50 per cent. of 137 pigs [61], 13 per cent. of 1,000 pigs [76], 20 per cent. of 1,722 pigs [31]. The writer has examined 4,457 lungs originating from 32 herds in 15 counties; 1,284 lungs, *i.e.*, 29 per cent. of lungs, and all except three of the herds were found to be infected with lungworms. The method used by the writer to detect lungworms [29] has been found to be effective in 97 per cent. of cases [30]. The diaphragmatic lobe was cut across about 1 inch from the posterior tip and an attempt made to squeeze lungworms from the cut bronchioles. In addition, lungs showing areas of emphysema or consolidation were examined in more detail.

Clinical signs. Clinical signs are usually mild, pigs developing a cough about three weeks after infection. Signs are more obvious in young animals and the writer has seen groups of animals heavily infected with lungworms and showing severe and persistent coughing. No signs are normally detected in chronic infections in which a few parasites persist near the tip of the diaphragmatic lobe, and in these cases there is little interference with the health of the animal.

Macroscopic pathology. The characteristic lesions are pale raised square or wedge-shaped areas of emphysema affecting the lobules particularly those of the diaphragmatic lobe near the posterior tip and free border, *i.e.*, those areas where the bronchioles are blocked with parasites or exudate. Areas of pneumonia associated with lungworm infection have been found in 11 per cent. of lungs examined by the writer. The consolidated areas are usually small but larger areas are not uncommon. Early cases are not particularly characteristic but well-established lesions are nodular (due to the formation of lymphoid follicles). Where emphysema, chronic bronchitis and parasites are present diagnosis is not difficult.

TABLE I
DISTRIBUTION OF LESIONS IN 602 CASES OF LUNGWORM PNEUMONIA

Lobes affected	Number of cases	Percentage
Diaphragmatic	503	83
Diaphragmatic + anterior	62	10
Anterior	37	6

The incidence of lungworm pneumonia in the anterior lobes is higher than these figures suggest because such lesions must often be masked by the presence of other types of pneumonia of the anterior lobes.

Microscopic pathology. The main features by which lungworm pneumonia may be recognised are:—

1. A chronic bronchitis in which the normal epithelium is replaced by mucous goblet cells, and in which the subepithelial tissues are infiltrated with eosinophils.
2. Hypertrophy of the smooth muscle of the bronchiolar and alveolar walls.
3. Hypertrophy of the peribronchiolar lymph follicles which form large distinct nodules of lymphoid tissue.
4. The presence of parasites, parasitic larvae or eggs which are frequently associated with giant cells.

The writer's findings agree closely with those previously reported [30, 31].

Epidemiology. Earthworms act as the only known intermediate hosts in the life cycle of *Metastrongylus* spp. The earthworm is known to live for as long as 10 years and to harbour viable metastrongyle larvae for many months [1]. The rearing of pigs on permanent pasture usually results in heavy lungworm infection; indoor systems of management reduce lungworm infection. However, even pigs housed permanently in concrete pens or yards may eat wandering earthworms and thus acquire lungworm infection.

Diagnosis. The most useful methods for demonstration [30], and assessment of the lungworm infection are:—

1. Identification of metastrongyle eggs in pig faeces by means of a magnesium sulphate flotation technique.
2. The demonstration *post-mortem* of parasites in the lung.
3. The identification of the characteristic lungworm pneumonia and the histological examination of these lesions.

Discussion. Outdoor systems of management which are often indicated in the control of the infectious chronic respiratory diseases of pigs, *e.g.*, virus pneumonia and atrophic rhinitis, favour an increase in the incidence of lungworm infection. Conversely most systems of management that reduce the degree of lungworm infection increase the opportunity for the spread of other chronic respiratory diseases of pigs. The clinical signs of all these diseases are similar enough to be confused with each other. It is relatively easy to demonstrate lungworm infection in most herds but the aim should be to assess the significance of this infection in the respiratory disease under investigation.

(c) The Aspiration Pneumonias

Following the aspiration of material there is a cellular reaction directly associated with the aspired material and also a mechanical interference with the normal defence mechanisms of the respiratory tract. Frequently there is secondary bacterial invasion.

Two principal types of aspiration pneumonia have been encountered by the writer.

(i) *Pneumonia Associated with Aspired Vegetable Material*

A type of pneumonia which appears to be caused by the aspiration of small fragments of vegetable material, has been seen by the writer in two pig herds. From these herds 323 cases of pneumonia of the anterior lobes have been examined microscopically and 57 cases have shown a similar histological picture. Fragments of vegetable material or their apparent remnants have been found in 40 of these cases. A similar condition has been reported in calves [95]. There have been only slight clinical signs associated with uncomplicated cases of this type of pneumonia in the pig. However, in both these herds cases of acute pneumonia have occurred which appeared to be secondary to the mild aspiration pneumonia.

Pathology. The consolidated areas usually affect the anterior lobes. In uncomplicated cases the lesions are often characteristic and consist of several small collapsed non-oedematous areas. The lesions in extensive or complicated cases are not usually characteristic. Microscopically pieces of vegetable material surrounded by multinucleated giant cells, are found in the bronchioles and alveoli. In some cases the foci are encapsulated but usually the lesions are more diffuse. In nearly all cases there is considerable alveolar collapse. The inflammatory reaction is usually chronic but it may become acute when secondary bacterial infection occurs.

(ii) *Pneumonia Associated with Upper Respiratory Tract Infection*

In two herds known to be free from virus pneumonia the writer has seen outbreaks of rhinitis accompanied by secondary pneumonia presumably caused by the inhalation of catarrhal or muco-purulent exudate from the upper respiratory tract. The pneumonia has involved the anterior lobes. Microscopically there has been blockage of bronchioles with exudate resulting in alveolar collapse. In some cases a secondary bacterial pneumonia has occurred.

(d) Acute Bacterial Pneumonias

Primary acute bacterial pneumonias appear to occur only occasionally in pig herds which are not affected with a chronic respiratory infection. Secondary acute bacterial pneumonias are frequently seen in herds of pigs where chronic respiratory infections occur. These pneumonias are mentioned in other parts of this paper.

2. Primary Respiratory Diseases of Uncertain Aetiology

(a) Virus Pneumonia of Pigs (Enzootic Pneumonia of Pigs)

Virus pneumonia is a disease in which the principal clinical sign is a chronic non-productive cough and in which the main pathological lesion is a pneumonia of the anterior lobes. Although a number of other diseases may show a similar clinical and pathological picture, virus pneumonia is characterised by its epidemiology. It appears that this type of pneumonia is the most commonly occurring respiratory disease of pigs in this country and similar pneumonias have been reported from many other countries. There are not yet any specific means of comparing these pneumonias and although there are minor differences between the descriptions of these diseases they do share many important common features. These apparently closely related diseases have been described under the following principal names: Ferkelgrippe (enzootische pneumonie) [51], Ferkelgrippe [52, 53, 64], Influenza-like disease [44, 45], Infectious pneumonia [24, 40, 41, 71, 72, 73, 74], Virus pneumonia [3, 6, 8, 9, 11, 12, 13, 22, 23, 34, 55, 70, 96], Coughing pigs (virus pneumonia) [91], Virus pneumonia like [78], Enzootic virus pneumonia [46], Enzootic pneumonia (virus pneumonia) [18, 57, 94], Enzootic pneumonia [17, 47, 56, 58, 59, 97], Transmissible pneumonia [65]. The name Virus Pneumonia was adopted because the causal agent showed many features in common with the viruses. However, the nature of the causal agent is still uncertain and because of this the writer would prefer the name "Enzootic Pneumonia"—a name which indicates the epidemiological and pathological features of this disease and which is being used by a number of workers who are investigating the aetiology of the disease. But in view of the widespread use of the name "virus pneumonia" it would probably create less confusion to retain this title for the time being.

Aetiology. Bacteria-free filtrates of pneumonic lung are infective for pigs and the size of the causal agent has been estimated by testing the infectivity

of various filtrates for pigs [8, 34, 42, 51, 64, 97]. It has thus been demonstrated that the diameter of the smallest infective particle varies between 200 and 450 mμ [8, 97]. Suspensions of pneumonic lung which have been treated with antibiotics are infective for pigs; established cases of pneumonia cannot be cured by the antibiotics at present available but establishment of infection can be prevented by the oxytetracycline group of antibiotics [8, 13]. These findings suggested that the causal agent is probably one of the larger viruses. The author has found an extracellular pleomorphic organism of similar size, in Giemsa-stained impression smears prepared from lungs of both experimental and naturally occurring cases of virus pneumonia [97]. This pleomorphic organism does not appear to be present in other types of pneumonia and it seems to be closely related to the pleuropneumonia-like organisms (PPLO) as judged by morphology, staining reactions and occurrence [97]. From cases of virus pneumonia an organism of similar morphology and staining reaction has been isolated in tissue culture by Swedish workers [56, 94]. Suspensions of tissue cultures containing this latter organism produce pneumonia in pigs [59], but pig-to-pig transmissions have not yet been attempted [60]. Pleuropneumonia-like organisms have been isolated from the respiratory tract of pigs affected with virus pneumonia, various other respiratory diseases of pigs and also from normal animals [19, 20, 21, 23, 88, 97]. Experimental inoculations of cultures of pleuropneumonia-like organisms have not produced pneumonia [20, 23, 97]. The relationship between the various organisms (*i.e.*, virus, organism isolated in tissue culture, pleomorphic organism and pleuropneumonia-like organisms) described by various workers has not yet been established. At present no definite conclusions can be drawn regarding the rôle played by these organisms in the aetiology of virus pneumonia.

Bacteria are not essential in the causation of virus pneumonia, but they are important particularly in field cases of the disease. A high proportion of cases of virus pneumonia are bacteriologically sterile. From those containing bacteria, pasteurella organisms are most commonly isolated. Amongst other organisms isolated are Friedlander's bacillus, *Haemophilus*, diphtheroids, coliforms, streptococci and moulds. Adult parasites and larvae of *Metastrongylus* spp. are commonly found associated with lesions of virus pneumonia. It has recently been shown that migrating Ascaris larvae increase the severity of the disease [93].

Clinical Signs. Virus pneumonia is a disease whose prominent sign is a chronic non-productive cough. The incubation period (judged by the onset of coughing) usually varies between 7 and 30 days but some pigs develop pneumonia without showing obvious signs. The onset of the disease is gradual and affected animals may cough for weeks or months. There is gradual recovery; some animals recover completely; others apparently recover but may still harbour the infective agent. Most affected animals show no obvious malaise but are unthrifty; experiments with one strain of virus pneumonia showed that the disease reduced the efficiency of food conversion and depressed growth rate [9, 11]. Some pigs develop an acute pneumonia in which bacteria often play a secondary but important rôle. Mortality is low even in these acute cases which usually make an apparent recovery, but may remain chronically affected. Virus pneumonia is more severe when pigs are housed under crowded conditions, and when it is newly introduced into a herd.

Pathology. The pathological picture described below has been seen by the writer in the majority of cases of pneumonia from 24 herds in which virus pneumonia occurs and a similar pathological picture has been seen in 5 experimentally transmitted strains of this infection [97]. Similar findings have been reported by other authors [46, 65, 70].

Macroscopic pathology. The lesions are usually confined to the respiratory tract and associated structures. Although the causal agent can be isolated from all parts of the respiratory tract, the macroscopic lesions are usually confined to the anterior and inferior lobes. The consolidation in these areas where the bronchioles are vertical is probably the result of exudates accumulating more readily in these areas. Macroscopic pneumonia is not usually detectable in experimental infections before the 7th day post-infection. In early cases there is a patchy consolidation of the anterior lobes; the pneumonic tissue is not clearly demarcated from the healthy tissue. The lesions are pale pink or grey in colour. A catarrhal exudate is present in the bronchioles and the cut surface of the lung exudes an oedematous fluid. About 3 weeks post-infection the lesions are usually more extensive and darker in colour, and are becoming more sharply defined. The affected areas become less oedematous and partially collapsed as recovery occurs and there may be complete healing. During the active infection there is enlargement and oedema of the local lymph nodes. In cases complicated by bacterial infection the pneumonic lesions become more extensive and often there is pleurisy or pericarditis. In such cases during healing there is formation of scar tissue and consequent distortion of the affected lobes.

Microscopic pathology. The principal change is an accumulation of mononuclear cells in the perivascular and peribronchiolar tissues. This change is usually detectable within 7 days of infection; it becomes more marked as the infection progresses and as recovery occurs the accumulations of mononuclear cells become smaller and more clearly defined. In cases complicated by bacterial infection the changes typical of the primary infection can often be detected although sometimes they are completely masked.

Immunity. No protective antibodies have been demonstrated in the sera of recovered animals [8, 53, 58], although apparently recovered animals are resistant to experimental reinfection [8, 58, 97]. Field evidence suggests that if recovered animals are exposed to a heavy and continuous infection they may be reinfected [14, 98], but there is no conclusive evidence on this point.

Attempts to immunise animals by inoculation of suspensions of whole pneumonic lung intrapleurally, intraperitoneally or subcutaneously (*i.e.*, routes of inoculation which do not cause pneumonia) did not

protect against experimental infection [8]. Suspensions of highly infective lung inoculated intradermally do not cause any allergic reaction [8, 97].

Epidemiology. Once the causal agent is established in the respiratory tract it may persist for many weeks or months [6, 34, 46, 52]. In some animals the pneumonic lesions and the clinical symptoms persist, but many animals recover clinically while still harbouring the infective agent. Some animals become infected and develop pneumonia but never show obvious clinical signs of the disease [60, 98]. It has not been possible to transmit virus pneumonia to animals other than the pig (except one successful transmission to the ferret, [8]) and there is, to date, no positive evidence to indicate other species acting as reservoir hosts. Fomites appear to play little part in the transmission of infection [8].

Virus pneumonia has only been produced experimentally by inoculation of the causal agent directly into the respiratory tract. Inoculation of infective material subcutaneously, intradermally, intravenously, intraperitoneally, and intrapleurally has not produced pneumonia [8, 97].

The causal agent leaves the animal body *via* the respiratory tract in the form of droplets (which are expelled in large numbers during coughing, sneezing and "talking"). Premises which had been left uncleaned and unventilated and which had been vacated 24 hours previously by pigs with virus pneumonia, did not infect healthy pigs [97]. Premises vacated only 10 minutes previously did infect 1 of 2 pigs exposed to risk [8]. Field and experimental evidence [98] indicates that the disease is not highly infectious and that more than a slight exposure to risk is necessary to initiate infection. There is an apparent difference betwen the infectiousness of different strains [98].

The morbidity is high but the mortality is low. The crowding of animals has a marked effect on the clinical evidence of the disease. It is most obvious when animals are housed in large communal houses and least obvious when animals are housed in relatively isolated conditions. There is no marked effect of season on the incidence of the disease nor is there any evidence of any breed resistance.

All ages of animals are equally susceptible to virus pneumonia. When an infection is newly introduced into a herd the older animals are often affected more severely than the young stock. In herds where the infection has occurred for some time the young fattening animals are most obviously affected, probably because (a) they are kept under crowded conditions and (b) the older stock has already had experience of the infection. Breeding stock running out of doors rarely show obvious signs of the disease.

Diagnosis. No tests have yet been developed for the specific diagnosis of this disease.

The clinical picture is not particularly characteristic. The histological picture is typical but not diagnostic—other pneumonias usually, but not always, show a different histological picture [97].

Thus the diagnosis of the disease is not a simple matter. Often the disease picture in the field is considerably complicated by the presence of secondary agents, and of other respiratory diseases which may mask the primary changes. Also the disease picture is very different under different conditions of management [97]. In individual cases diagnosis is almost impossible. However, it is possible to make a diagnosis on a herd basis by using all the available information.

In herds where virus pneumonia occurs there are a number of features which may be recognised which, when combined, enable one to make a diagnosis. The clinical picture is useful, particularly when observations can be made on groups of animals. The epidemiology of virus pneumonia is characteristic. The disease is usually most obvious in pigs kept in large groups. A series of examinations *post-mortem* of lungs of bacon and pork pigs which have been housed in a communal fattening-house, reveals a high incidence of pneumonia of the anterior lobes. Where laboratory facilities are available the histological examination of a number of cases should be made. Examination of stained impression smears made from pneumonic areas indicates the types of organisms involved in the infection; when combined with cultural examination of lungs it indicates the degree and nature of secondary bacterial infection. Where practicable, experimental transmission of the disease should be attempted to give information on the infectiveness of the disease and to indicate the incubation period, the clinical signs and the gross and microscopic pathology of the experimental disease. If possible the size of the causal agent should be estimated by filtration.

Treatment. No methods of treatment which are effective against the primary agent are known but the tetracycline group of antibiotics will prevent the establishment of infection [13, 57]. Antibiotics will not cure established cases but they do reduce the severity of the disease [13, 16, 17, 18, 67] and are of particular help in acute secondary bacterial pneumonias. The treatment of chronic cases with the antibiotics at present available is of doubtful value.

Control. In view of the difficulty of diagnosis and the high proportion of subclinical cases it is not possible to control the disease by merely eliminating affected stock. There seems to be little possibility of developing a satisfactory vaccine.

The effects of the disease can be minimised by providing good conditions of management, and housing animals in small isolated groups to reduce the spread of infection and increase the chances of recovery [98].

Absolute control may be achieved either by total replacement with healthy stock or by eradication of the infection [3, 12, 96]. Some success has been achieved in the eradication of infection from herds by using a method which consists of the following steps:—

(a) Selected sows are farrowed in a sufficient degree of isolation to prevent the transmission of airborne infection from one pen to another.

(b) The sow is removed from the pen when the litter is 8 weeks old but the litter is retained in isolation for a further 4 weeks. During this 12 weeks the litter is continually observed for any clinical signs of respiratory infection.

(c) Two piglets are sacrificed from each apparently healthy litter to check that there is no pathological evidence of respiratory infection.

(d) Several litters judged to be healthy are grouped, but the group is retained in isolation and kept under continual observation.

(e) When the pigs reach marketable weight, the gilts not retained for breeding and the hog pigs are slaughtered and examined *post-mortem* for evidence of respiratory infection.

(f) The remaining gilts and boar pigs judged to be free from virus pneumonia are used to establish a new herd.

(b) Atrophic Rhinitis

Atrophic rhinitis occurs in many countries and is said to cause severe economic losses [85]. However it is not a disease which has been clearly defined; the principal lesion by which it is recognised (*i.e.*, atrophy of the turbinate bones) is merely the end result of an inflammatory reaction which may be caused by a variety of agents and conditions. However, there does appear to be a specific infectious atrophic rhinitis though other conditions may resemble it both clinically and in morbid anatomy. Work on the disease has been reviewed and discussed by Switzer [87] and Gwatkin [43].

Rhinitis in Great Britain. In the 3 years (1954-6) since atrophic rhinitis was made a scheduled disease, 23 outbreaks have been confirmed in Landrace and Landrace X pigs. Amongst our indigenous pigs mild rhinitis is common [26, 36, 98] and occasionally a more severe disease is seen, which is similar clinically and pathologically to infectious atrophic rhinitis [98, 36]. Done [25] has identified a relatively common form of rhinitis which he provisionally named " Inclusion Body " rhinitis. The disease is usually mild but a chronic rhinitis may supervene, with consequent destruction of the turbinates.

A condition occurring in both Landrace and non-Landrace pigs in the Isle of Man and Northern Ireland which was indistinguishable pathologically from atrophic rhinitis has recently been described [49]. 10 per cent. of 1,000 snouts examined showed varying degrees of abnormality. Twisting of the snout was only observed in Landrace pigs.

The relationship between these various diseases is not clear.

Aetiology of atrophic rhinitis. There has been little correlation between the findings of different workers in different countries. It seems probable that a number of conditions, resulting in a similar clinical and pathological picture, is being described. Some of the findings have been as follows:—

1. In Great Britain it has been suggested that the indigenous rhinitis may be caused by a virus because of the occurrence of virus-type inclusions and a lymphocytic inflammatory response [25].

2. In America one form of atrophic rhinitis is caused by a filterable agent of size similar to that of the larger viruses, small rickettsia and pleuropneumonia-like organisms (PPLO) [89]. This agent is sensitive to terramycin but not to penicillin and thallium acetate.

3. In Canada, Scandinavia and America some forms of atrophic rhinitis do not contain this filterable agent and only unfiltered material is infective [33, 43, 89]. This non-filterable agent is sensitive to penicillin and streptomycin.

4. In Denmark deficiency of Vitamins A and D is thought to be an important factor in the aetiology of atrophic rhinitis [5].

Various organisms have been isolated from cases of atrophic rhinitis and although no simple causal relationship has been found a number of organisms are thought to play some rôle in the disease.

(a) Pasteurellae are frequently isolated, and pure cultures have experimentally produced turbinate atrophy [33, 89, 43]. This experimental disease, however, does not transmit by contact.

(b) Pleuropneumonia-like organisms (PPLO) are frequently isolated [88, 89, 19], but cultures have not produced the disease. Similar organisms have been isolated from normal animals.

(c) Many other organisms have been isolated and a number have produced atrophy of the turbinate bones following their inoculation either alone or in combination with pasteurellae or PPLO. The principal organisms concerned are *Corynebacterium pyogenes, Pseudomonas pyocyanea, Fusiformis necrophorus,* streptococci, *Haemophilus* and trichomonads.

Signs of Rhinitis. The incubation period is usually 10 to 21 days. Young animals are more liable to show clinical signs, and if older animals are exposed they may become infected without the disease being obvious and without atrophy of the turbinates occurring. The common clinical signs are sneezing, snuffling, rubbing of the nose, nasal discharge, conjunctivitis and overflow of tears due to blockage of the *ductus ad nasam.* The dried tears cause a brown stain which spreads from the inner canthus of the eye down the face. Epistaxis occurs in the Scandinavian disease, is common in the American disease but is rare in the rhinitis seen in Great Britain. In severe cases of the disease there may be blockage of the nasal passages due to the accumulation of inflammatory exudates which results in mouth breathing and/or exaggerated respiratory sounds. In chronic cases the severe nasal distortion may interfere with normal respiration. There is sometimes a secondary inhalation pneumonia [97] associated with coughing. Intercurrent infections (*e.g.*, virus pneumonia) increase the clinical severity and the losses resulting from the disease [4, 86].

Pathology. There is a catarrhal inflammation of the mucous membrane of the nasal cavities and associated structures, with resorption of bone and failure to form new bone [77]. It appears that varying degrees of turbinate atrophy and malformation of the nasal bones and septum occur according to the severity and chronicity of the inflammatory process [26]. In mild cases, changes are hardly detectable; in severe chronic cases the turbinate bones disappear completely and the malformation of nasal bones results in distortion of the face. There are no specific macroscopic pathological features. Microscopically there is destruction of glandular elements and replacement of bone with fibrous tissue [77]. In "Inclusion Body" rhinitis in Great Britain, the occurrence of characteristic intranuclear virus-type inclusions in the serous

glands of the mucous membrane has been decribed [25].

Epidemiology. In its epidemiology atrophic rhinitis very closely resembles virus pneumonia. The causal agent is only known to infect *via* the respiratory tract, and once established the agent persists for long periods, even after clinical recovery. Field evidence suggests the development of only a low-grade immunity and it appears that recovered animals may become reinfected [26]. Animals which recover clinically and even animals which show no evidence of previous infection may harbour the infective agent. Non-apparent infections occur particularly in older animals. Although the causal agent may become established in all ages and types of animals, turbinate atrophy and nasal distortion occur in only a small proportion of cases and usually only in animals which have been exposed to infection when they are growing rapidly [26]. So, if one uses turbinate atrophy and facial distortion as the criterion of infection one would draw the erroneous conclusion that only young animals are susceptible to the infection and that the disease is only serious in the fine-boned (*i.e.*, Landrace type) pigs.

Apparently recovered animals are sometimes responsible for the introduction of infection into a herd. Thus the source of infection may be difficult to trace especially as it can be several years before the disease attains full significance and is recognised [85]. The causal agent does not survive for long outside the pig and premises are thought to be safe after 3 months' rest [32].

Morbidity is high but mortality is usually low [25]. The crowding of young animals increases the clinical evidence of the disease [98].

Diagnosis. Three conditions (or variations of the same condition) can be recognised relatively easily:—

(a) Mild non-specific rhinitis (by clinical and *post-mortem* examination).

(b) "Inclusion body" rhinitis (by histological examination of suitable material).

(c) Rhinitis resulting in atrophy of turbinate bones (by *post-mortem* or rhinoscopic examination).

The assessment of the significance of the rhinitis is very difficult. Whether the disease becomes obvious and important depends not only on the causal agent but on a number of other factors (*e.g.* conditions of housing, feeding and age and breed of animals). Since a wide variety of agents can cause rhinitis and subsequent defective bone formation and since the causal agent of infectious atrophic rhinitis may not always cause turbinate atrophy it is not possible to identify the occurrence of a specific disease solely by the finding of this non-specific lesion. The *post-mortem* findings must be correlated with the severity of the disease and particularly the epidemiological characters of the disease. With an ill-defined disease of such an insidious nature as atrophic rhinitis it may not be possible to make a diagnosis without careful examination over a period of time and consideration of all the available information.

Discussion. Conditions of pig management in Great Britain are favourable to the spread of respiratory infections (as judged by the incidence of pneumonia) yet there does not appear to be a rhinitis comparable in severity with the disease occurring in Scandinavia [97] and in the U.S.A. [14]. But even if identical agents were responsible for the atrophic rhinitis in different countries one might expect differences in the manifestations of the disease, because of influencing factors such as different systems of management, housing and climate, different breeds of pigs and the presence or absence of important secondary organisms.

There is not yet sufficient evidence available for one to be able to draw any definite conclusions regarding the relationship of these various similar diseases.

3. Diseases which affect other Organs but which also Affect the Respiratory System

(a) Pneumonia Associated with Swine Fever

Pneumonia and respiratory symptoms have been known for many years to be commonly associated with swine fever [50], and inflammatory lung changes have been found in 15 per cent. of experimental cases and 45 per cent. of field cases of swine fever [48]. Experimentally the virus may infect pigs *via* the respiratory tract and pneumonia is produced and can be serially transmitted [66]. There have been reports of outbreaks of pneumonia in Morocco [35], [68], [69] and in France [37], in which a strain of swine fever was suspected to be the aetiological agent. In one herd in Britain that the writer has observed for several years and which is free from virus pneumonia an outbreak of swine fever was associated with the occurrence of pneumonia in the "in contact" pigs.

The presence of other characteristic signs of the disease may make one suspect that the pneumonia is due to swine fever. Ideally specific diagnosis may be made by experimental transmission combined with specific protection tests using vaccines or immune serum. The swine fever virus will pass Seitz EK filters and will infect by various routes of inoculation. It should therefore be possible to tell whether the pneumonia is caused by the swine fever infection alone or whether other pneumonia-producing agents are also involved.

(b) Pneumonia Caused by Migrating *Ascaris lumbricoides* Larvae

It has been thought that under field conditions *A. lumbricoides* larvae during their migration through the lung cause increased respiration rate, coughing and pneumonia. However, as far as the writer is aware there are no reports of experimental ascariasis in pneumonia-free pigs in which there has been an imitation of what presumably occurs in natural infection, *i.e.*, the feeding of small repeated doses of *A. lumbricoides* eggs. Thus although there are numerous reports regarding the development of pneumonia following the feeding of *A. lumbricoides* eggs it is not possible to relate these findings directly to field conditions.

Experimentally, pigs fed a single large dose of *A. lumbricoides* eggs develop a cough and respiratory embarrassment 4 to 8 days later but these signs only persist for a few days [10], [75], [90]. Pigs killed 7 to 8 days after infection show haemorrhages throughout the lung and there may be consolidation of the

anterior lobes. Taffs has shown that these signs and lung changes are less severe in the immune animal in which fewer larvae reach the lung [90]. Pigs originating from a herd which was free from pneumonia but infected with *A. lumbricoides*, had not developed a pneumonia of the anterior lobes when killed between 5 and 21 days after feeding a single large dose of viable eggs [10].

It has been shown recently [93] that if eggs of *A. lumbricoides* are fed to pigs which have a slight and inapparent virus pneumonia, the pneumonic lesions become more extensive.

It seems probable, that in the field, ascaris larvae migrating through a normal lung produce only slight respiratory signs, but that if the pig is already affected with pneumonia the migrating larvae may be important in increasing the extent and severity of this pneumonia.

Diagnosis of Respiratory Infections in Pigs

It is relatively easy to recognise the existence of broad pathological and clinical conditions, but extremely difficult to make a precise diagnosis, particularly as a number of respiratory infections often occur simultaneously. Even with laboratory facilities it is not simple to make a diagnosis because of the paucity of knowledge of several of the common conditions. Although no scheme can be entirely satisfactory, the following suggested procedure may help in making a diagnosis of the respiratory disease occurring in the herd.

Preliminary epidemiological considerations

A study of the epidemiological behaviour of the disease correlated with the system of management is an essential preliminary to accurate diagnosis. Decide whether the respiratory infection has been present for some time or whether it is a new outbreak. Find if animals have been introduced into the herd and whether they could have brought in the disease. If the herd is self-contained, has the respiratory infection become evident following a change in the system of management? The system of management has a most important bearing on the opportunity for spread of a disease and its clinical evidence. If pigs are housed in the open air in small groups under relatively isolated conditions, chronic respiratory infections may be present in the herd without being recognised. On the other hand if animals are housed under intensive conditions the circumstances are ideal for the spread and maintenance of respiratory infections. In most herds, fattening pigs and sometimes even breeding animals are housed under conditions which favour a high incidence of respiratory infections.

Diagnosis. Is the condition acute or chronic?

An acute disease involving many animals in the herd almost simultaneously, may be swine influenza. The incubation period is short, the clinical signs and the course of the disease are characteristic and there are specific means of diagnosis.

Sometimes an acute respiratory disease involving many animals is seen when an agent which usually causes a chronic disease is introduced into a fully susceptible population. The acute disease gradually subsides and the chronic form of the disease emerges. Unless the history of the herd is known it may not be possible to distinguish between this latter case and that in which an acute infection becomes superimposed on an already existing chronic respiratory disease.

With an acute disease involving one or a few animals it must be decided whether the cases are (a) sporadic acute infections (in the writer's experience these are relatively rare) or (b) acute cases flaring up in animals already affected by chronic respiratory disease (these cases are quite common and appear to include the majority of the acute respiratory infections in pigs).

The chronic respiratory infections are common in pigs and include the 3 important diseases or groups of diseases (a) rhinitis, (b) virus pneumonia (c) parasitic infections.

First decide whether the upper respiratory tract (*i.e.* the nasal cavity, trachea and bronchi) or the lower respiratory tract (*i.e.* the lungs) is principally involved. With an upper respiratory tract infection the clinical signs are mainly sneezing, snuffling and nasal discharge, and with a lower respiratory tract infection, mainly coughing. There may be overlap in symptoms as well as in lesions; a secondary pneumonia may accompany a primary rhinitis; a rhinitis may be caused by an infection whose primary lesion is pneumonia. Also look out for signs which would indicate only secondary involvement of the respiratory tract, *e.g.*, in swine fever or ascaris infection.

Post-mortem examination is necessary to check the clinical impressions. It is worth sacrificing a few selected pigs: animals of about 10 weeks old which are showing mild signs are usually most suitable for this purpose. (To obtain pathological material which is easy to examine the best method of slaughter is to anaesthetise the pig first with nembutal intravenously, and then to bleed it to death from the carotid artery.) In animals of this age lesions are more easily recognised; rhinitis will probably be recognisable macroscopically, and there has been sufficient time for atrophy but not for marked regeneration of turbinates to have occurred; if the condition has primarily involved the lung there will have been opportunity for pneumonia to have become established or for metastrongyles to have reached maturity.

If pigs have been fattened in a large communal house the examination *post-mortem* of such animals at the bacon factory gives a most useful guide to the type of respiratory infection occurring in the herd. The incidence of turbinate atrophy may be seen; with virus pneumonia a high proportion of lungs show pneumonia of the anterior lobes. However when animals have been housed in small isolated groups there may be little evidence of these respiratory infections at bacon weight. The severity of metastrongyle infection will usually be independent of the degree of crowding during the fattening period.

By the microscopic examination of pathological material, particularly from early cases, the specific or general features of the disease may be recognised,

e.g., intranuclear inclusions in "Inclusion Body" rhinitis, perivascular and peribronchial accumulations of mononuclear cells in virus pneumonia, metastrongyles associated with the typical histological picture in lungworm pneumonia. Several different respiratory infections may occur concurrently, thus to assess the principal condition it is essential to examine pathological material from a number of animals. The microscopic examination of pathological material is a most useful aid to diagnosis, even though lesions caused by different aetiological agents may sometimes be indistinguishable histologically (*e.g.* the non-specific picture that is associated with virus pneumonia may occasionally be found in other types of pneumonia).

If facilities are available attempts should be made to transmit the disease experimentally. The sporadic respiratory infections do not appear to be readily transmissible. However, rhinitis, virus pneumonia and swine fever pneumonia can be transmitted experimentally. In these cases one can estimate the size of the causal agent by filtration, determine which routes of inoculation result in infection and also compare the incubation period, clinical signs and gross and microscopic pathology with those of the natural disease.

Ideally, the final diagnosis of the disease depends on the identification of the causal agent. Unfortunately the nature of the causal agents of the common chronic respiratory diseases of pigs have not been well established. Thus in most cases a precise diagnosis based on identification of the causal agent is not possible.

Summary

Some of the respiratory diseases of pigs in Great Britain have been described, and the diseases selected have been either the ones commonly encountered or those of particular interest. The diseases have been divided into 3 groups: (a) the primary respiratory diseases of known aetiology, (b) the primary respiratory diseases of uncertain aetiology, (c) the diseases which affect other organs but which also affect the respiratory system. Precise diagnosis is difficult because of the inadequacy of our knowledge regarding some of the most important diseases. The main features of the diseases have been described and an attempt has been made to show in individual diseases, firstly how a tentative diagnosis can be made by studying the clinical and epidemiological picture and the gross pathology, and secondly in which instances laboratory studies are of help in making a more precise diagnosis. Finally a procedure has been suggested which may be used in determining the type of respiratory infection occurring in a herd.

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THE SPEAKER'S INTRODUCTION

Mr. Whittlestone said that he wished first to thank the organising committee of the B.V.A. for giving him the opportunity of presenting the paper. The present time seemed particularly appropriate for discussion of the respiratory diseases of pigs because there was a need for some basis on which different workers could compare their findings, and the discussion which was about to take place might help in that respect. Also, much clarification was necessary regarding the occurrence of the various diseases and their relative importance.

There was little need to point out the complexity of respiratory diseases of pigs. Possibly those who were not thoroughly familiar with the subject found the paper a little confusing. That was inevitable because not enough was known about respiratory diseases of the pig for him to be able to present a simple description that was not misleading. A number of respiratory diseases which he had encountered, but about which he knew very little, had deliberately not been mentioned. Workers elsewhere had encountered other types of pneumonia and it was hoped that something would be heard of these pneumonias in the discussion.

In thinking about respiratory diseases of pigs, he personally had found it a great help and consolation to consider the complex situation of respiratory diseases in other animals and the unsatisfactory state of knowledge. He had been fortunate to know and to have had considerable help from Dr. Chu, as well as to have been familiar with his work on chronic respiratory diseases of poultry.

It would be worth their while to pay a further visit to the Scientific Exhibition to see the demonstration, prepared by Dr. Chu and his colleagues, on chronic respiratory diseases of poultry. There they would see a diagram showing the diseases which affected the respiratory tract of poultry and would appreciate that the position was extremely complex. As more evidence came to light regarding respiratory diseases of pigs the resemblances between the diseases in the two species became striking, and it would seem likely that the group of diseases in the pig would prove to be just as complex as that in poultry.

It should be stressed that diagnosis of respiratory infection was not an easy task, because of the lack of knowledge. Even in the laboratory there were not yet any simple diagnostic methods for most of the conditions encountered. In all cases it was necessary to study at least the clinical, epidemiological and pathological features of the disease. The importance of the epidemiological picture should be emphasised. Obviously very much more work was needed to clarify the methods of diagnosis.

Mr. Whittlestone offered a word of encouragement to the practitioner. By an intelligent examination of all the information which was available to him, the practitioner should be able to reach a broad diagnosis of the type of respiratory infection occurring in the herd. The practitioner was the person who was in the position to assess the significance of the disease he recognised, to decide which measures were economically justifiable, and, more important, to decide which control measures were practicable on that particular farm.

In the section of the paper which dealt with virus pneumonia in pigs there was outlined a method which was suitable for the control of the chronic respiratory infections. A method of that type was devised for the control of Ferkelgrippe in Germany. Waldmann and Radtke (1937) reported considerable success in its use. At the present time this method was being used in Sweden to control enzootic pneumonia. Professor Beveridge, Dr. Betts and the speaker had used a similar method in Cambridge and had achieved some successful results. However, if complete success were to be achieved, it was a method which must not be undertaken lightly. In their experience, complete eradication of the chronic respiratory infections was achieved only when it was attempted on a small scale, where suitable premises existed or could be constructed, and when the owner himself was determined to achieve success. It was certainly not a method which could be forced upon the farmer.

With regard to lungworm infection, it would be noticed that the incidence that he had found was higher than that recently reported by Dunn. Most of the bacon-pig lungs he had examined originated from herds in which attempts had been made to control virus pneumonia. As a result, the piglets had been reared in isolated pens, usually on pasture, and so they had had ready access to earthworms. Therefore, one might expect a rather high incidence of lungworm infection. (Applause.)

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The Opener

Mr. W. A. Noble, in opening the discussion, said that he would like to congratulate the author on presenting such an excellent paper. It must be obvious to all those who had read the paper that to cover such a wide subject in such detail must have taken hours of research. To those who had not yet read the paper he recommended it for most serious perusal.

He found the author and himself were standing at opposite sides of the pigsty, so to speak, for while the author saw the various conditions through the eyes of a research worker, he saw them through the general practitioner's eyes; and it must be admitted that, on the last day of Congress, his eyes were probably a little bleary.

As a general practitioner who had neither the time nor facilities for detailed microscopical examination, he had

to rely more on clinical observations and macroscopic *post-mortem* appearance, and must always bear in mind that the advice given to clients and the treatment prescribed must be as economical as possible and yet produce results. From that practical point of view, in a pig practice situated in the Fens, he would be forced to alter the author's order of primary diseases of known aetiology and place them in the following order:—

1. Bacterial pneumonia.
2. Aspiration pneumonia.
3. Lungworm infections, with swine influenza last.

In view of the fact that at Cambridge there was being bred a race of disease-free pigs, in order to enable evaluation of the significance of the various viruses which were encountered in a pig's respiratory tract, it was possible that the opinions of the author of the paper and the opener of the discussion on it would, at the end of the year, be like a too fat hog and not grade very well.

A fairly common and devastating acute bacterial pneumonia encountered was due to Pasteurella. Incidentally, that condition was met with in fat bullocks, which it could kill so quickly that one was always suspicious of anthrax. However, they were concerned that morning with pigs, and bullocks were mentioned only to show that pasteurellosis could exist in animals without the aid of the virus of pig virus pneumonia. Often sudden death was the first sign of that condition. In pigs the in-contacts went off food and appeared hypersensitive, with a temperature usually between 105° and 107° F. There was some swelling of the throat region and there might be a slight oedema of the upper eye-lids. *Post-mortem* examination revealed acute pharyngitis; subcutaneous C.T. in the neck appeared, and cyanotic lymph glands were swollen and red. The outer surface of the lung in the less hyper-acute cases showed a marbled effect due to infiltration of the intertubular septa with a pale red serious fluid. The most successful treatment he had found so far was large doses of soluseptasine with serum to all animals off food, and serum to in-contacts.

B.H.S. was another disease cropping up in the Fens. The whole herd might be affected to a greater or less degree. The symptoms in sows were a slight cough, a watery discharge from the eyes, and the skin was hidebound. They returned to hog or produced small and weakly litters. At *post-mortem* the lungs of those young pigs were oedematous and had a superimposed acute congestion most marked on the dorsal aspect of the apical and middle lobes. Treatment of sows with an autogenous vaccine produced very satisfactory results. Could the author give them an idea of the incidence of that disease?

Aspiration pneumonias were met with and were most common in weak and recumbent pigs. The end result was a septic bronchial pneumonia. It might be interesting to note that coccidia had frequently been found in the lungs of young pigs from herds with a heavy coccidial infection. Vomiting was fairly common in the latter stages of the disease, and no doubt some of the stomach contents became aspirated into the lungs. How long did the author think the foreign material had been in the lung in his uncomplicated cases? Mr. Noble would have thought that there would inevitably be an acute secondary pneumonia from fragments of foreign matter being aspirated into the lungs.

The author said that lungworm infection was rather heavy. It was not as great a menace in pigs as it was in cattle. That was probably accounted for by the fact that pigs were usually kept indoors on concrete, or in crew yards which were not suitable habitats for lumbricus parasites either major or minor. Mr. Noble had only once recognised the condition clinically and that was in a group of gilts which were running out at grass. By taking them into a yard their coughs cleared up.

He had often seen in slaughter-houses the lesions in pigs' lungs so well described by the author, but could not agree that one had only to cut across the diaphragmatic lobe about 1 in. short of the posterior border and squeeze the lungworm out in 90 per cent. of cases. They were difficult for him to find and he was pleased to know that some of the author's colleagues in Cambridge had the same difficulty.

Like the author, he had never seen a field case of swine influenza and that was why it was placed last in importance.

On primary diseases of uncertain aetiology, he strongly supported the author's view that, at least for the present, they should keep to the term " virus pneumonia of pigs " to save confusion as there were about a dozen different names for the condition. They were all so well acquainted with the disease, and the *post-mortem* picture which the author gave, that doubtlessly all members having pig practices were puzzled by the degree of virulence which was associated with it and wanted to know whether there were various strains of the virus.

Waldman had found the organism as a saprophyte in 10 per cent. of normal pigs while working on enzootic pneumonia in Germany. In young pigs kept in poor conditions, as well as in those in the modern large fattening houses with several hundred pigs under one roof, the disease could cause a big headache for the general practitioner. Yet, under good conditions, and where there were fattening boxes for about a dozen pigs per box, clinical virus pneumonia in pigs seemed to be self-eliminating. Unlike the author, Mr. Noble found that in untreated animals kept under the former conditions the mortality rate could be high when acute pneumonias developed. Penicillin itself was useless in their treatment, but its synergistic effect when combined with streptomycin was quite good, and the acute pneumonias responded to antibiotics of a wider spectrum than penicillin.

The author said that suspensions treated with antibiotics were infective to pigs, that the conditions could not be cured by antibiotics when once established, but that the establishment of infection could be prevented by dosing pigs with antibiotics of the tetracycline group. From that it was reasonable to conclude that there was some unknown factor or condition that must be present in the pig before it could contract virus pneumonia. It was possibly a secondary subclinical bacterial infection which was susceptible to the tetracycline group of antibiotics, or was it yet another unidentified virus which was tetracycline-susceptible that was causing the mischief? What was the preventive dosage rate of the tetracyclines? The feeding of antibiotics in low dosages as a routine was to be deprecated, and trials had so far shown that no antibiotic appreciably increased the food conversion ratio when corresponding controls were kept under ideal conditions.

Since swine atrophic rhinitis had become a scheduled disease Mr. Noble had been very worried as to how it could be recognised. It was pleasing to learn from the author that the condition had not yet been clearly defined. One often came across isolated cases of sows with long faces and the snout twisted to one side. It was probably due to faulty bone formation, and if there were only occasional isolated cases in the herd it did not cause undue concern.

About 6 years previously Mr. Noble had come across an atrophic-like outbreak in a herd of pigs, some 30 animals being affected to varying degrees. The symptoms were those the author had described: sneezing, snuffling, nasal discharge, and in one or two pigs there were even traces of blood. If the animals were hustled there were signs of respiratory distress. Later, some showed nasal distortion. In some snouts the turbinates were almost completely atrophied, while other animals developed a type of bulldog snout. The clinical appearance of some was indistinguishable from that on coloured plates made during an outbreak in the United States. The condition was not transmitted experimentally and it was thought at the time that trichomonads which were isolated from nasal washings were the cause. There had been two smaller outbreaks since which occurred only in hot, dry weather in the summer.

How was the reported scheduled disease confirmed or refuted by the Ministry?

Pneumonia was often associated with swine fever, but, over and above the lesions in the thorax, lesions were found in the abdomen. At *post-mortem* he had never seen a pig in a herd where swine fever was either suspected or confirmed, in which there was only a pneumonia with no lesions in the bowel. Bowel lesions were not always well marked, but there was always at least a varying degree of lymphadenitis of the mesenteric glands with small, scanty

haemorrhages in the endothelium of the colon and/or caecum, but one had to look most carefully for them.

The migrating Ascaris larva was an important cause in aggravating virus pneumonia, but was it as common as most people believed? Adult ascarids, in Mr. Noble's experience, were found in only about 8 per cent. of pigs. What were the views of others on that?

It was, he agreed, impossible to be 100 per cent. accurate in diagnosis in view of the paucity of knowledge of some of the conditions and the fact that there was usually an overlapping of causative agents. Epidemiological considerations, as mentioned by the author, coupled with *post-mortem* findings and smears from mediastinal lymph glands and heart's blood did help in sorting things out. Fortunately for the general practitioner, modern antibiotics often gave at least an apparent clinical cure for acute bacterial flare-ups of chronic respiratory diseases which, after all, were the most common types of pneumonia in the pig.

The General Discussion

Dr. W. M. McKay (London). "I should like to congratulate Mr. Whittlestone on a very excellent paper, and would like to make it clear at the outset that I am not associated with the company about which Dr. Betts complained regarding claims for one of the antibiotics in the prevention of virus pneumonia in pigs.

"I would venture to interpret, if I may, Dr. Betts's remarks on the failure of antibiotics to prevent virus pneumonia in pigs as meaning that the use of antibiotics in the feed did not prevent the actual development of the virus injury to the lung tissue itself. In other words, the virus entity was not prevented.

"I do not think he will dispute, however, that any farmer who has used antibiotics in pig foods will say quite categorically that since using an antibiotic his losses—that is his clinical losses, not deaths, but the actual loss of condition in the infected animals—have been considerably less. I think it is the general experience that the use of a broad spectrum antibiotic is of considerable help in reducing losses from virus pneumonia.

"One other point I would like to make is this, on what appears to be the vexed question of atrophic rhinitis in pigs. Those of who are familiar with the pig industry in Denmark, and who have seen many cases of atrophic rhinitis in pigs in that country would say that it would be impossible that it should exist in this country and remain undetected. Those of us who were involved in the major outbreaks of foot-and-mouth disease in this country during the war, and who between us examined many thousands of pigs' snouts conscientiously could not possibly have missed such a classical picture. The peculiar concertina effect on the skin and the twisting of the snout to one side or another is unforgetable, and it would be quite impossible for pigs suffering from this disease not to be detected. I am aware, of course, that in Denmark and Sweden they say that the disease existed in this country long before the importation of pigs from Sweden which are incriminated in our recent outbreaks; but I feel confident that this is not so. No one who has once seen atrophic rhinitis can forget it, or fail to detect and diagnose it."

Dr. Braude (Shinfield). "Following the contributions of Dr. McKay and Mr. Gellatly, I would like to mention, as a layman, that I have seen unmistakable symptoms of atrophic rhinitis in pigs abroad, including many cases in the Large White breed. In my experience over the last 20 years (and I must have seen hundreds of thousands of pigs), I never saw similar cases in this country before the recent importations from abroad, and I cannot accept the view that cases may have been missed for lack of looking for them—one simply could not miss them.

"I think it is unfortunate to bring the breed controversy into this field. There appears to me, as a layman, to be a complete lack of knowledge of the basic factors involved, and until a little more is known and the basic factors supporting the arguments have been established, greater discretion is needed in making public pronouncements which incite controversy."

Dr. N. S. Barron (Reading) asked for further information regarding the ideal environment within a piggery to ensure or reduce the ravages of V.P.P. He pointed out that the recent Northern Ireland work had considerably confused the issue. Were we now to advise on damp, dark, warm houses, or were we to follow the more orthodox and somewhat more logical approach to the problems? He thought that perhaps Professor Lamont might be able to answer this, but would also be glad of the speaker's views.

Whilst he considered that the Cambridge approach to eradication was scientific and logical it was, at times, not altogether practicable, owing, amongst other things, to cost and labour difficulties. Even where the breeding stock were affected he found that the disease could be reduced to a bare minimum if housing conditions were satisfactory, and that many farmers "lived with the disease" without suffering any serious economic loss. Some stated they suffered none at all. He felt that the atmosphere should be dry, that temperatures should not fluctuate, pigs should be kept in small numbers within walls at least 5 ft. high, or, preferably, running to the ceiling, and that the common practice of mixing pigs from different litters to get uniform batches, was one of the great dangers and should be avoided during the period of attempted eradication. Each litter should be run through to bacon weight as a unit.

Professor Lamont (Belfast) congratulated Mr. Whittlestone on his very useful contribution to our knowledge. He would like to make the point that it was easy to be critical of the administrator, particularly when one did not have the responsibility of deciding a problem. He would point out that in 1937 Professor Waldmann and Dr. Köbe had shown Mr. Shanks and himself outbreaks of atrophic rhinitis in North Germany. When they returned to Belfast they had examined a very large number of herds of pigs without seeing anything remotely resembling the condition they had seen in Germany. He (Professor Lamont) had also seen atrophic rhinitis in Canada. Nothing like the Canadian disease had been seen in Northern Ireland. It was perfectly true that when one examined a sufficient number of specimens in the abattoir occasionally one found noses of pigs with absence of turbinate bones and facial distortion. Enquiry on the farms from which the specimens came revealed no evidence or history of disease similar to what occurred in the Landrace pig. The problem therefore for the administrator was that a serious disease existed in the Scandinavian countries, no similar clinical disease was observed in the British Isles, should free importation of pigs from Scandinavia be permitted with the underlying danger to home bred stock? Obviously until the research worker clarified the picture and provided a sure foundation for the administrator to build on there was no option but to schedule atrophic rhinitis.

He would like to ask Mr. Whittlestone if he considered swine fever pneumonia as a distinct lesion. He felt that he could recognise swine fever pneumonia and found it a very helpful point in building up a diagnosis.

Professor W. I. B. Beveridge (Cambridge). "I would like to congratulate Mr. Whittlestone on his paper. He has made important contributions in two directions. Firstly, he has made an intensive study of the pathology of pneumonias of the pig and has gone a long way towards defining more clearly the entity we know as V.P.P. and differentiating it from various other conditions with which it may be confused. Secondly, he has discovered an organism which probably is the cause of V.P.P. Although he does not claim yet to have established that this organism is the causal agent he has in fact a considerable body of evidence that it is. There seems to be a good prospect that in the near future Mr. Whittlestone will solve the difficult problem of the aetiology of this disease and so establish a firm basis for further progress.

"While I agree with Mr. Lamont and certain other speakers that sometimes the only advice we can give to a farmer who is troubled with virus pneumonia is to improve the housing of his pigs, I cannot agree that ideal housing will completely abolish the adverse effects of virus pneumonia. Our experiments at Cambridge do not support such a view. Improved housing will no doubt enable the infected pig to perform better than under poor housing, but with improved housing and V.P.P.-free pigs the performance is even better. One cannot say merely by examining V.P.P.-infected pigs that they are not handicapped by the disease. The effects of virus pneumonia on growth rate and food conversion are insidious and often not obvious;

they can only be determined by doing controlled experiments where these factors are carefully measured over a period of months."

The Reply

Mr. Whittlestone, in replying to the discussion, said that he hoped to be forgiven if he did not deal adequately, in the short time left, with all the points that had been raised. Mr. Noble was thanked for his contribution and for viewing these diseases from the standpoint of the practitioner. In the author's experience, acute bacterial pneumonia occurred extremely infrequently in herds which were free from chronic respiratory infections. The aspiration pneumonia which he had seen appeared to have been in existence since the pigs were on the sow.

As to changes in the virulence of infection of virus pneumonia, there were no methods of comparing strains and, therefore, he could not answer the question directly. There were, however, factors which appeared to affect the virulence. The first factor was the system of management. Where pigs were kept under intensive conditions the disease would be a serious problem; where they were kept in small isolated groups, under good hygienic conditions, the infection would apparently disappear completely. If they were absolutely free from virus pneumonia, it was quite possible to put 500 pigs together without any evidence of the disease appearing. The second factor which affected the virulence was the stage of infection. If the disease was newly introduced into a herd it would be much more severe than if it had been present for some years. The third factor was the nature and extent of secondary bacterial infection.

The question on antibiotics had been adequately answered by Dr. Betts.

Those who had spoken on rhinitis were thanked for their contributions. Professor Lamont's remarks in that connection were particularly appreciated. There had been a great deal of criticism of the Ministry for their policy on the disease, but they had a most unenviable task in dealing with it. Mr. Whittlestone had recently seen outbreaks of rhinitis in Scandinavia which were far more severe than the outbreaks occurring in Great Britain. It was quite possible that the disease which occurred in this country was different from that which occurred in Scandinavia and on the American continent. Every attempt should be made to control the spread of the infection. Mr. Kerruish's remarks about rhinitis in the Isle of Man would seem to give further support to the view that the condition with which he was dealing was different from that which occurred in Scandinavia.

With regard to Professor Lamont's question on pneumonia in relation to swine fever, Mr. Whittlestone said that his experience was not as great as the Professor's. He had experience of only one outbreak of swine fever in a herd free from virus pneumonia, and that, of course, did not provide a basis on which to give a general opinion. (Applause.)

Mr. Noble, also in reply, said that in his experience the type of pig house which accommodated a lot of pigs under one roof did spread virus pneumonia. The best type of house used in the Fens originated in Ireland, and Professor Lamont had spoken about it several years previously. It housed about a dozen pigs and, in its design, everything was done to conserve heat in winter. The cost of keeping pigs in that way was about 6d. per pig per week if 200 pigs were kept on the farm.

On the question of feeding antibiotics, he had not inferred that any antibiotic cleared up virus pneumonia. It was not an economical consideration. (Applause.)

The Relationship of Soundness and Conformation in the Horse

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THE examination of horses as to soundness and, above all, their selection as to suitability, is part of the work of veterinary surgeons which requires sound judgment and the employment of knowledge tempered with experience. It is a melancholy fact that, to-day, such work is done by fewer with confidence and satisfaction.

When asked to present a paper to this meeting on some aspects of soundness in the horse I willingly accepted, and the title of the paper indicates the importance I attach to conformation and its influence on soundness. After many years' experience, not not only in the examination of horses, but also in their selection and purchase, one naturally becomes dogmatic—a healthy dogmatism—because it develops from experience and from the accumulation of an amount of information which is stored in the mind, and of which use is made almost automatically by the person concerned. The relationship between soundness and conformation has long been recognised.

> "A horse is sound when he is free from hereditary disease, is in the possession of his natural and constitutional health and has as much bodily perfection as is consistent with his natural formation.
>
> "The rule as to unsoundness is, if at the time of sale or examination, the horse has any disease, which either actually does diminish the natural usefulness of the animal, so as to make him less capable of work of any description, or which in its ordinary progress will diminish its natural usefulness; or if that horse has, either from disease (whether such disease be congenital, or arising subsequently to birth) or from accident undergone any alteration of structure that either does at the time or in its ordinary course will diminish the natural usefulness of the horse, such horse is unsound."

Conformation is the manner in which the horse is formed or put together. Bad conformation may not be unsoundness in itself, but it may often lead to unsoundness. The study of conformation should consist of the appraisement of points of structure and the estimation of their significance in the horse as a whole. Let us now consider what we require as broad principles of conformation.

In the first place the horse, whatever his breed or job, should convey to the eye suitability in make and shape, with no obvious fault which would upset the whole make-up. In short, the horse must have "presence"—that undefinable something which, at first impact to the eye, impresses one with the suitability of the horse for his particular work. If the horse meets you well and, on a cursory inspection, shows no outstanding faults of conformation, it is more than likely that, on further examination, the horse will be more or less sound. It is "presence," allied with good movement, which enables one to pick out the first half-dozen in a strong class in the show ring, or rapidly to select a few animals of the right type in the busy atmosphere of a crowded sale yard and then proceed to a more detailed examination.

The Head and Neck

The head should be of a size proportionate to the size of the horse itself, with a straight face line and well defined features. The forehead should be broad, full and flat, and the ears of medium size, finely pointed and carried alertly. The eyes should be prominent, clear and large, with eyelids of uniform curvature. The muzzle should not be too fine, the nostrils large but not dilated, with thin lips and the incisor teeth sound and regular. The lower jaw should be well defined, clear at its angle, and the space between the two branches of the lower jaw should be wide in order that the larynx may be fully accommodated, with room for large muscular attachments. Any deformity of the jaw, such as a parrot mouth or an under-shot jaw is an unsoundness depending entirely on a fault of conformation. Such horses are bad-doers as a rule, and require additional care in feeding. In the case of breeding animals a faulty conformation of the jaw may be passed on to their progeny. The width between the branches of the jaw is an established feature of the Arab horse and one to which great importance is attached.

The angle at which the head meets the neck is one of the most important features of conformation. If this angle is too acute, the head and neck are not not well set on; in the extreme, a "cock-throttled" appearance is shown. By the acuteness of this angle there is the possibility of compression of the larynx, with consequent interference with respiration. When, in such a case, the depth from ear to throat is also marked, it is suggestive of commonness or "jowliness" and such a horse is not likely to bridle well or to carry his head kindly when ridden or driven. An over-large head is objectionable in that it places a strain upon the forehand, and it will mean that more muscular power from the great muscles of the neck is required to maintain it in position. Such horses often tire easily and "die" on the hand when ridden or driven.

The neck should be of proportionate length, reasonably crested but not too heavy, and its muscular development should be in proportion to the work the horse has to do. A long, lean neck on the Thoroughbred and riding horse is desirable; a shorter, well-muscled neck is an essential part of the draught horse and prepares the collar area for the reception of the draught. The carriage of the head is very largely

determined by the shape and nature of the neck and, moreover, the junction of the neck with the body determines, very largely, the slope and carriage of the shoulder. Actually, the neck of the draught horse is rarely very short, but the muscular development of the neck and crest may make it appear to be somewhat shorter in proportion, for example, to that of the riding horse. The jugular groove should be easily determined, and in the well-bred horse the trachea should be well marked out.

The withers should be of good height and well defined. Too high a withers is undesirable and is sometimes associated with deficient spring of the chest; whilst a low, thick, heavy withers is undesirable in the light horse and interferes with the free mobility of the shoulder. In the Hackney, a low, thick withers is usually associated with deficient action and a bad shoulder, and whilst a strong withers is desirable in the draught horse, too low and fleshy withers result in the saddle not maintaining its correct position and there is a tendency for the collar to rock. It should be noted, however, that some very good Arab horses may be found to have a rather low withers.

The Chest

The chest should be deep and full, the ribs should be long, well-sprung and spaced well back, so that the edge of the last rib is not too far away from the point of the hip. Flat, narrow ribs are undesirable and tend to reduce the capacity of the chest. Such horses are often poor doers, due to there being insufficient room for the heart and lungs. If too narrow, not only will the horse have no heart room, but the two forefeet will emerge from the body placed too close together and give rise to the dealer's expression "both legs coming out of the same hole." If the chest is too wide, the horse will be found to have a rolling gait, will paddle with his forelegs, and will be found to waste a considerable amount of muscular action when endeavouring to walk freely.

Measurement of girth is of the greatest importance, and in a horse of 16 hands a girth measurement should be required of at least 6 ft. At one time, when purchasing a large number of horses for travelling long distances daily in double harness, I was instructed by the director of the firm that I must never purchase a horse that had not 6 ft. of girth. It was maintained, quite rightly, that this was the minimum measurement that gave the heart and lungs room to function adequately when the horse was in hard work.

A prominent sternum is sometimes encountered. This is a conformation which I dislike intensely; it gives the horse a pigeon-breasted appearance and is often seen in ill-balanced horses whose forefeet are too much under the horse. It is often associated with a flat chest and insufficient heart room, and such horses are often bad-doers when put into hard work.

The Back

The back should be short and strong, but it must be remembered that the relative shortness of the back must be governed by the work the horse has to do. The Thoroughbred and riding horse must have some length of back if they are to travel quickly; whilst the draught horse must be short of back and be closely coupled. The term "long back" is often used loosely. A horse for fast work must have some length of back and the confusion arises when the length of the back and the length of the loin are not defined. It is the loin which must be as short as possible in all circumstances; the loin is the least supported portion of the back and it is the horse with the length of loin which particularly gives the impression of slackness and too much length behind the saddle.

In the conformation of the back one may have a hollow back, in which the back is unduly dipped (and which must not be confused with the hollowing of the back with old age); and the roach back, in which there is an upward curve of the back and loin. Both are undesirable, and in my time I have noted a number of roach-backed horses who have eventually turned out to be shiverers. Horses with odd conformation of the back very often do not lie down regularly when in the stable and so shorten their working life. Particular care should be taken when examining so-called "cold-backed horses." Some of these horses may have an abnormality of the withers and saddle-bearing area and only very careful examination will reveal this. Often, such an abnormality may not be noted on palpation of the withers and saddle area. It may be discovered by standing behind the horse and viewing along the back to the base of the neck. Any alteration in the shape of the withers or saddle-bearing area is then more easily detected. I regard the "cold-backed" horse with dislike and one should never omit to draw the attention of the purchaser to the disability, which may amount to unsoundness (Van Raalte *v.* Fitzroy, 1956).

The belly should be proportionate to the size of the horse, but not too big. The horse in training will show a tendency towards lightness of the abdomen, particularly as he approaches the peak of his work, but this must not be confused with the very sharp narrowing of the belly known as herring-gutted, which usually indicates poor condition, with insufficient room for the abdominal contents. Such horses are often of nervous temperament, difficult to get fat and often tend to scour when at work. In the draught horse, a good capacious belly—or as it is sometimes termed colloquially, "bread basket"—is indicative of a good constitution and of a good feeder; when needed for long hours of work such a conformation is essential.

In all geldings, of any breed, always look for a well-developed sheath. It is a practical point that lack of development of this appendage usually indicates a weak constitution and, again, such animals are often bad-doers.

The croup is an area of great importance in conformation. It comprises that part of the body between the loins and the setting of the tail. The pelvis and sacrum are involved in its formation and so effect a compact connexion between the hind leg and the trunk. In most cases a nearly horizontal croup is ideal and, indeed, is requisite for the development of great speed; but in the draught horse, a more inclined croup will fill the requirements of

ability to shift weight. In a nearly horizontal croup, the tail is well set on, whereas in the draught horse the tail may appear to be somewhat lower owing to the inclination of the croup.

The Fore Limbs

The shoulder, in proportion to a good withers, should be of ample length and slope. No other portion of the horse's anatomy comes under greater criticism than the shoulder and opinion on the type and suitability of the shoulder may vary with different individuals. Ample slope is essential in any breed of horse and a good shoulder is as essential in the draught horse as in the Thoroughbred. Ample length in the shoulder is required in order that there should be plenty of room for the insertion of large and powerful muscles. Moreover, full action of the shoulder cannot be attained unless there is sufficient length of back to accommodate its obliqueness. Upright shoulders give rise to a shortened gait and, indeed, to undue concussion of the whole of the foreleg, whilst in many cases an upright shoulder is associated with a horse standing over in front—a combination that will eventually diminish his usefulness. The arm should be suitable for the attachment of its large muscles and, in all cases, should be as long as is proportionate to the shoulder; whilst the elbow should stand clear of the body and be well defined. Elbows that are turned in are objectionable, as they result in the feet being turned out and, in the opposite tendency, the feet are turned in. In both cases undue strain is directed to the fetlock and feet, and both conditions tend to produce lameness in the lower part of the leg and in such cases speedy cutting and interference are common faults.

The forearm should be long, wide, thick and well developed. From the point of view of speed, the conformation should be such as to present a long forearm and a comparatively short cannon. In the Hackney with high knee action, the forearm will be found to be comparatively short but it should be remembered that if the forearm is too short, the action will be of a choppy nature and will not produce sufficient freedom to allow the horse to move with pace *and* action and to reproduce that impressive one, two, three, four, which is so desirable and essential.

The knee should be as large as is compatible with the size of the horse and it should be flat and free from any suggestion of roundness. In reason, the larger the knee the better, more articular surfaces are provided and concussion is absorbed. Small round knees are very objectionable and cannot play their part in absorbing the weight of the horse and the concussion of the ground. The knee may show several objectionable aspects of conformation. For example a calf knee is undesirable and does not absorb concussion; additionally the calf knee is ill-fitted to resist the over-extension of the knee which occurs in fast work. The amount of over-extension of the knee which may occur during a 'chase or fast-run hurdle race is amazing and, in the fraction of a second, when the horse is alighting, an enormous strain is temporarily thrown upon the knee which may be in a position of over-extension. Calf knees are often "tied-in" below, with insufficient room for the flexor tendons. Any lateral deviation of the knee is a serious breach of conformation. Such conditions give rise to unequal distribution of the body weight and tend to produce injuries to the supporting and connecting ligaments as a whole.

A markedly forward direction of the knee is known as "over at the knee" or "knee-sprung" and it may be congenital or acquired. Many young horses with slightly forward knees are very sure-footed and have great freedom of movement. When acquired, this conformation is usually the result of excessive work combined with contraction of the tendons and such horses will frequently stumble and be unsafe to ride.

The cannon should be short and strong with width from front to back and this gives a good measurement of "bone" below the knee. Nevertheless, it should be remembered that in the long run, it is not the amount of bone, but the quality of it which really counts. The cannon of the draught horse is shorter than that of the thoroughbred and in all well-formed animals the metatarsus is always longer than the metacarpus. The tendons must be clearly defined, with no suggestion of "gumminess," and when viewed from the front, cannon, fetlock and pastern must be in a straight line. No conformation is more likely to lead to unsoundness that a round cannon bone, with fleshy tendons; such legs will not stand up to hard work.

The fetlock should be wide, thick and free from blemishes. When the fetlock is narrow in the antero-posterior direction, the tendons are always closer to the cannon bone and become more subject to strain at work.

The pastern should be of medium length and slope and both extremes have their draw-backs. The excessively long pastern, which is often low-jointed, is weak, and not only does it throw great strain on the tendons but it is an important factor in the production of sesamoiditis. The short upright pastern is very strong, but it absorbs concussion to a greater extent and may result in the early formation of ring-bone *if* associated with an indifferent foot. There is no doubt that the worst combination met with in the pastern is that of excessive length and low-jointedness. This conformation in the hind limb is sometimes associated with a straight hock and stifle and is one of the worst conformations of the draught horse that I know of. It leads to trouble with the hock joint which is subjected to excessive strain above and below, whilst the tendons of the hind limb rapidly show evidence of strain. In such a conformation the hind leg, throughout its length, has no mechanism for relieving the concussion of the ground.

The Feet

Perhaps in no other part of the body is conformation related to soundness more closely than in respect of the feet. Xenophon, centuries ago, pointed out the importance of the foot in the horse and insisted that in all cases of examination of the legs, one should look first at each foot. With defective feet the

usefulness of the horse is diminished, and whatever the job he does his working life is limited, and eventually disease or inability will make its appearance. Feet must be of a similar size and odd feet must arouse suspicion at once. I will admit that, occasionally, a horse may be found which has had odd feet since birth, but for all practical purposes the odd-footed horse is an unsound horse. A good foot must be well shaped, not too large or too small, with a strong, deep and wide heel and a well developed frog and, preferably, the colour of the horn should be dark or blue. Seen from the front, a well-developed foot should present a level surface, free from rings or grooves, and showing no tendency to contraction at the quarters. Remember that any form of contraction is an unsoundness. When lifted, the foot should present a deep, wide heel with a good frog having a shallow, medium lacuna. Any difference of the angle of the slope in the wall of either foot should be regarded with suspicion.

McCunn has drawn attention to the important significance of any "waisting" of the hoof, accompanied by a lateral groove in the wall on either side. Such a foot is almost invariably unsound and a horse with such a foot usually develops some form of pedal ostitis.

I dislike a frog with a deep, split-up cleft, particularly in the draught horse; such feet, in my opinion, frequently develop thrush or canker. *Of all faults in conformation of the feet, a weak heel is the worst, because, without a sufficient depth and width of heel, no horse will remain sound for long.* Such a conformation exposes the navicular area to injury and particularly does it encourage injury to the wings of the pedal bone, resulting in ostitis.

The foot may appear to be an excellent one when viewed from the front, but the real test of its value is to see whether it possesses sufficient depth of heel. A narrow hoof head should be avoided and in this connexion it is always essential, in heavy horses, to raise the hair at the coronet in order to examine the top of the hoof. A horse with a narrow hoof head, with a tendency to bulge slightly on its anterior aspect is likely to develop pyramidal disease or low ringbone when put to hard work. Flat feet are weak feet, and horses with such rarely remain sound for any length of time. It should always be remembered that on the foundation of the horse's feet rests its upper structure and I would quote the edict of H. Bouley:—

> "The foot is the veritable foundation of the animal edifice and this should always be remembered in the purchase of a horse. It is the region in relation to which one cannot be too fastidious. Is it defective? Is it diseased? One can then foretell the severe wearing out and ruin of the animal, as well as considerable expenses of shoeing and treatment. On the contrary, is it duly constituted? Is it healthy? Every day, the animal will resume, without discomfort, the work of the day before. He will never be incapacitated in work, for it is in the inferior regions that the members begin to blemish and, all the more slowly, as the extremities are better conformed."

It is useful to remember that in many cases, the horse with indifferent feet will begin to prefer the centre of the road and will avoid the extreme camber of the near side.

The Hind Limb

The hind limbs are the essential elements of propulsion in the horse and are associated with groups of muscles larger and more powerful than those of the forelimb. It has been pointed out that the greater obliquity of the shoulder and the more horizontal position of the croup in horses of speed, tend to diminish the scapulo-humeral and coxo-femoral angle and so facilitate the forward and backward movement of the limbs. The thigh should be long, well-muscled and deep and well let down. Looked at from behind it should be thick, with ample muscular development, and above all, it must not show any signs of a split-up appearance. In this respect one should remember the old axiom of "a head like a duchess and a bottom like a cook." The second thigh should be well developed, and the stifle should be well forward in position.

In the Thoroughbred horse, length from the point of the hip to the hock is necessary for speed and, generally speaking, the greater this length the more speedy the horse. Meyrick Good has for some years annually compiled the essential measurements of many of the Derby colts and these are of the greatest interest to students of conformation. In 1956 the first three in the Derby ("Lavandin," "Montaval" and "Roistar") had measurements as follows:—

	Height	*Girth*	*Bone*	*Hip-Hock*
"Lavandin" ...	16.1	75	9	43
"Montaval" ...	16.3	70	8¾	42
"Roistar" ...	16.1	74	8	40
	(Time 2 mins. 36 2/5 secs.)			

It is interesting to compare these measurements with another outstanding horse, namely the heavyweight horse "Mighty Atom," probably among hunters one of the greatest horses of the century. Here we note the enormous depth of girth and heart room, associated with sufficiency of bone and a fair length from hip to hock.

	Height	*Girth*	*Bone*	*Hip-Hock*
"Mighty Atom"	17.1	86	9¾	42

A very well grown 3-year-old shire colt, standing 18 hands high had the following measurements:—

	Height	*Girth*	*Bone*	*Hip-Hock*
"C Whats Wanted"	18	84	12½	42

Another good type of heavyweight horse, with excellent conformation, showed the following measurements:—

	Height	*Girth*	*Bone*	*Hip-Hock*
"Langley Gorse"	16.2	76	9½	40

Whilst an outstanding show pony—"May Day" measured:—

	Height	*Girth*	*Bone*	*Hip-Hock*
"May Day" ...	13.2	65	7½	36

The Hock

This constitutes the most important joint in the process of propulsion, and a good, well-developed and positioned hock is essential for soundness. The hock should be big in proportion to the size of the horse, wide and deep, with a well-marked point and, above all, well supported beneath and with no "tie-in" immediately below. Above all, the nocks must be a pair and remember that the strong hock found in the young horse may fine down with increasing age. A slender, narrow hock is bad, just as a full, round, fleshy hock must be disliked. The true value of the hock, apart from its size, depends upon the greater or less inclination of the tibia above and the cannon below. The so-called "sickle hock" results in the cannon bone taking an inclination forward so that the hind leg is brought under the body. Such a conformation is most undesirable. It leads to excessive strain of the hock joint above and of the tendons below, and such a conformation usually results in unsoundness. In all cases, however, it must be remembered that for draught horses, the hock may have a little forward inclination compared with that of the riding horse. This "sickle hock" conformation is sometimes found in a big horse standing over in front. Such a horse will usually be a source of trouble, either from over-reaching or pulling off his foreshoes when galloped. The condition known as "cow hock" is objectionable and is often associated with other defects of conformation. As a result, the toes are turned out and loss of power and movement occurs as the limbs are moved outwards instead of forward in a straight line. "Bowed hocks" are equally objectionable, the hocks being set wide apart and the toes turned in. In this conformation, the animal will be noted to twist the hock out as the foot comes to the ground and the foot develops a screwing-movement as it touches the ground. In such animals, the hocks tend to develop thoroughpin and bog spavin, whilst the coronet and feet become upright. Such animals are very hard wearers on their shoes and the toe is invariably knocked out too soon. This screwing action of the foot on reaching the ground is particularly likely to produce lameness. A good hock should be large and well directed and in its relation from the point through the back of the cannon to the ground, should be vertical.

With regard to the limbs as a whole; in the fore-limb, looked at from the front, a perpendicular line dropped from the point of the shoulder should divide the leg and feet into two lateral halves. Viewed from the side, a perpendicular line dropped from the tuberosity of the scapula spine should pass through the centre of the elbow joint and meet the ground at the centre of the foot. In the hind limb, viewed from the rear, a perpendicular line dropped from the point of the buttock should divide the leg and foot into two lateral halves. Viewed from the side, a perpendicular line dropped from the hip joint should meet the ground midway between heel and toe.

Although movement in the horse is hardly within the compass of this paper, good conformation must be associated with correct movement. A horse must walk well, and if this movement is carried out correctly the horse will usually be satisfactory in his other paces. Action should be straight and true with no dishing, brushing or interfering, and the toe should be well extended, especially in the riding horse. In the active draught horse and the Hackney, the knees and hocks should be well flexed and carried from the forearm and thigh in a straight and forward direction. In these breeds the horse must move over the ground and not pick the feet up and put them down in the same place again.

The action of the Thoroughbred and riding horse should be low and sweeping, with extension of the toe and a good carry forward of the hind leg. Avoid a horse that goes on his heels—this is bad movement and will usually be found to be associated, sooner or later, with unsoundness.

Lastly, soundness of wind and conformation. That conformation may influence soundness of wind is, to my mind, undeniable. From the point of view of size and height alone, it is well known that a big horse, *e.g.*, a heavyweight hunter with height, is more likely to be unsound in his wind than a horse of moderate size. How many times do we examine a big, good-looking hunter and immediately in our mind wonder if he will prove to be a roarer or a whistler? The relative immunity of the pony breeds from roaring and whistling and the marked tendency of the fat, short-backed, wide-barrelled pony to become broken-winded is, indeed, well known.

The set of the head upon the neck also has some influence. The horse whose head meets the neck at an acute angle and who has excessive depth from ear to throat may be more susceptible to unsoundness of wind than another. Similarly, lack of space between the branches of the jaw to accommodate the larynx may result in its compression when the head is flexed. The Arab horse, whose freedom from unsoundness of wind is well marked, has great width between the branches of the jaw; indeed, this is one of the characteristics of the breed.

It must be remembered that not every whistler or roarer may have paralysis of the recurrent nerve, and conformation may, and in my opinion does, play a part in the production of such unsoundness.

Finally, "a good horse is one with many good, few indifferent and no bad points."

Never hesitate to buy a sound, well-made horse because he is in poor condition. Such horses, under good management and feeding, grow just as you could wish them to; and remember that fat or gross condition may hide a multitude of faults.

Without an understanding of conformation no one can develop that knowledge of soundness and unsoundness which is desirable in those who undertake examinations of the horse. It must never be forgotten that within the framework of its conformation, lies the horse's essential soundness.

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THE SPEAKER'S INTRODUCTION

Mr. Dawes said that the reason why he chose this subject was that he felt that even at this stage in the history of the country the time was ripe when one should pay attention to the problem of soundness in the horse. This problem was age-old and never varied. It was well to remind oneself that the question of soundness depended almost entirely upon the person conducting the examination of a horse, and it was that person's responsibility to his client that his examination should be thorough and should miss nothing which might have any bearing upon the history of the horse in question.

He had perhaps been rather dogmatic in his paper, but he felt that he had reached an age at which he was entitled to be dogmatic. His living during a period of 25 years had been bound up with this ability to select horses. He had always observed the rule of paying attention to his mistakes, for in horse practice one was never told about the good horses one had examined and selected; one was, however, continually reminded of " that awful brute you bought for me ten years ago."

It was a curious fact that any mistakes in the veterinary examination of horses were never buried. One could sometimes get away with mistakes in connexion with other domesticated animals, but a mistake made in the examination of horses as to soundness lived to reproach the examiner.

The author then showed slides of well-known horses, describing their characteristics. In all these slides he drew attention to what he called "great presence," presence being that indefinable thing which immediately drew one's attention to an outstanding horse. In showing slides of several famous Hackneys, he would like to remind his listeners that these great actioned horses of the past were not only ornamental but utilitarian and he had driven Hackneys for years in practice and had found them wonderful roadsters.

Mr. Dawes concluded his remarks by circulating a series of photographs of famous horses, with a brief description of their outstanding features.

The Opener

Mr. E. Brayley Reynolds, in opening the discussion, congratulated Mr. Dawes upon his practical approach to the subject. He was convinced from his own experience that conformation exerted a tremendous influence upon the continued soundness and ability of the individual horse.

It was evident that Mr. Dawes had in a great measure been in the fortunate position of being able to pick and choose his animal. But, the speaker asked, what proportion of veterinary surgeons in these days of mechanisation were asked to undertake such a task? The agricultural horse population in 1913, the year in which Mr. Dawes qualified, was 1,324,400, and last year it was 233,500. Might these figures in some way roughly indicate the probable proportion? Even the Ministry of Agriculture put "soundness" and "conformation" in separate compartments.

Mr. Dawes had quoted a definition for soundness and unsoundness, but for conformation to amount to an unsoundness under this definition it would have to amount almost to the degree of a congenital deformity. He later mentioned "parrot mouth" or "undershot jaw" as an unsoundness entirely a fault of conformation. Each was an unsoundness, but as a congenital deformity, and had no comparison to a "calf knee" or "sickle hock," for example, each of which was a fault of conformation but not necessarily an unsoundness.

The basic principles governing good conformation applied equally to all breeds. Mr. Dawes had summed up the appearance of the whole in one word—"presence." The word which the speaker had more commonly used and heard, certainly in connexion with hunters and racehorses, to convey the same impression was "balance." It conveyed perhaps a more specific meaning, and in two ways, namely, that the animal as a whole stood well balanced and that there was a good balance between the various parts, each approaching to the perfect. It was no use having close on perfect beauty in one part for it to be almost absent in another.

Mr. Dawes had dealt so thoroughly with his subject that from a general point of view there was little on which to comment and still less with which to differ. There was an old saying, " They go in all shapes." It was a pity that this expression was ever coined, for although it might be founded on apparent truth, it was a most pernicious statement, and in the majority of cases it was used to cover a multitude of sins. The speaker recognised that he might be told, " 'andsome is as 'andsome does," but his reply would still be " They would have gone better in a good shape."

He agreed with Mr. Dawes's remarks about the width between the angles of the bottom jaw—this space in the adult should comfortably accommodate the closed fist—but he differed from him with regard to the long, lean neck for the riding horse. The best judge of a Thoroughbred whom he had ever known used to say, " You cannot show me the Thoroughbred foal with too short a neck; it is sure to grow long enough. The great fear is that it will grow too long." The neck most to be feared to predispose wind unsoundness was the long, lean and arched or swan neck. The neck should be wide and muscular, particularly in its upper part when viewed from behind or above. Perhaps the best illustration of this was a picture painted by " Snaffles " with the caption " The finest view in Europe." It was a view, evidently from the saddle, of the pricked ears and the upper part of the neck of a grey horse and a formidable jump ahead.

Mr. Brayley Reynolds said that he appreciated that the flat ribbed horse was not generally liked, and experience would seem to justify this, but he wondered whether a girth measurement would really confirm that a want of heart room was a contributing factor to the inefficiency of an animal with this conformation.

Commenting on what had been said of the back, and loin, he quoted what William Osmer wrote more than 200 years ago when describing the Godolphin Arabian, one of the foundation stallions of the English Thoroughbred. He wrote: " Whoever has seen this horse must remember that his shoulders were deeper and lay further into his back than any horse yet seen. Behind the shoulders there was but a very small space before the muscles of his loin rose excessively high, broad and expanded, and which were inserted into his quarters with greater strength and power than in any horse I believe ever seen of his dimensions." It would be difficult to find a better description of what that region should be.

Mr. Dawes had stated, in connexion with roach-back, that he had seen a number of animals with this conformation become shiverers. In the days when the speaker was in closer touch with shires and other heavy horses it was not uncommon to see this conformation, and of such an animal it was said that it had had its back "pulled up." This was actually the case, and it had resulted from putting a too keen youngster too early to too heavy work, and was not a natural conformation. He had seen the same deformity occur in two-year-old Thoroughbreds. He wondered whether Mr. Dawes considered it likely that the shivering symptoms resulted from this injury to the spine, the induced misplacement of the vertebral column, causing interference in the region of the intervertebral foraminae.

Commenting on another aspect of the paper, he said he was surprised to read that a nearly horizontal croup was ideal and, indeed, requisite for the development of great speed. He was prejudiced against this conformation and was convinced that it tended to a loss of power by placing the posterior limbs behind the position most suitable for them to exert their best effort. By putting the posterior line of suspension of the body farther from its line of gravity, greater weight was put on the fore limbs, tending to affect their action and wear. His prejudice against this conformation had perhaps been strengthened by its great tendency to exert a harmful effect upon the stud life of the female possessing it. In fact, it could become a point of great importance in the examination of a mare for soundness for stud purposes.

Mr. Brayley Reynolds then dealt with the shoulder. Assheton Smith was reputed to have said, " Shoulders—meaning good shoulders—are not a necessity; they are a

luxury." If the judgment of what constituted a good shoulder could be reduced to a definite standard capable of being quickly and easily applied, a lot of argument and doubt would be avoided and much aid given to the novice. One that could be so used—it amounted to a law almost—was this: "The closer the humerus approaches to the upright, the better the shoulder." The so-called slope of the shoulder, or scapula, was not so important. In the majority of cases it did not vary as much as would seem to be thought, whereas the slope of the humerus directly determined the position of the fore limb as a whole, whether it was well forward and so capable of free action, or whether it was under the body giving rise to a more cramped action and greater concussion to the whole limb. An animal with this latter conformation was said to be heavy-shouldered and was less able to get its fore legs out of the way of its hind legs which were trying to do the work.

They had rightly been told that the fore arm should be long and the cannon short, as this had much to do with the ideal conformation of the fore limb. He was in agreement with this, but they had not been told by what standard to judge these lengths. It could only be in relation to one another, and to estimate their comparative lengths more correctly he suggested the making of a mental comparison of the distance from the elbow joint to the middle of knee with that from this point to the fetlock joint. Then, in a manner somewhat similar to that for judging the shoulder, "The greater difference between these two measurements, the better proportioned the limb." Conversely, the nearer these measurements approached to being equal, so had the animal a long cannon with correspondingly long, weak tendons more liable to sprain, and the action of the limb was more climbing than low and sweeping.

The knee joint was probably the most important joint of all in the Thoroughbred, chiefly perhaps owing to the age and speed at which these animals worked. The number of bones comprising the knee joint with their multiple facets at various angles and levels was one of evolution's wonderful pieces of mechanism for resolving the lines of force, or concussion. Even with the best formed knees, trouble could arise, and it was practically certain to do so in ill-developed badly formed knees. As had been said by Mr. Dawes, any lateral deviation of the knee was a serious breach of conformation. There was one type of this deviation to which he wished to refer because the tendency would appear to be on the increase in the lighter breeds. In calf-knee or bowed-knee the respective inward and outward lateral deviation was one of the vertical line of the limb at the region of the knee, but in the one that he had in mind it was an actual downward and outward deviation of the knee joint itself. The line of the downward force through the radius fell within the line of the upward force through the cannon instead of their meeting one another truly and being equally resolved within the knee.

On the question of short upright pasterns, in the lighter breeds the increased general concussion to the whole limb as a result of this conformation was likely to produce trouble in the knee joint even of good conformation.

One should not condemn too hastily or too severely the long pastern, even in cases in which the fetlocks were low. Alec Taylor, a trainer of great experience, maintained that he had yet to see too long a pastern, and he added that they never broke down. That, too, had been the speaker's experience. He referred to a yearling of which some people had said that they would not think of buying an animal with such long pasterns. It won the Derby and the St. Leger two years later. A long pastern was a more risky conformation, however, in the hind limb, and more so, as Mr. Dawes had said, when it was associated with straightening of the hock. Straight hocks were favoured by many, but they could be too straight. He did not confine the risk to the draught horse but extended it to the adult hunter and steeplechaser. He objected to it even more in the brood mare.

On the subject of feet, Mr. Brayley Reynolds said that a number of the progeny of some stallions, and some of the highest class of certain lines of blood, were born with odd fore feet, but if this were unaccompanied by any other questionable conformation of the corresponding fetlock or knee, then it was of little import, and the animal might remain sound throughout its career. He would not stress too much the necessity for a wide heel, particularly when the heel was shallow and weak. The really low, weak heal as seen in the adult was more the product of neglect or faulty appreciation of the rightful attention to that type of foot. A vicious cycle soon developed in a foot with this tendency. Such a foot differed from a genius in that it was made and not born. Bold but careful attention could preserve such feet. He wondered what proportion of animals born with feet having this tendency eventually became useless. As a rule they saw only those that had been neglected and become lame.

Less had been said of the hind limbs than of the fore limbs. This might be because unfitness for work as a result of trouble in the hind limb was not so frequent as in the fore limb, though it would be only guesswork to venture the proportion. He wondered whether Mr. Dawes had any views relative to conformation, or any other factor, tending to control this difference and whether he recognised any particular conformation likely to predispose luxation of the patella.

Mr. Dawes had said in his paper that a perpendicular line dropped from the point of the shoulder and the point of the buttock divided the fore and hind limb respectively into two lateral halves. This was the ideal conformation. To emphasise this point in connexion with the hind limb, it should be noted that almost without exception high-class sprinters, up to five and six furlongs, had this conformation. Races over these distances are run at such a terrific pace from start to finish that there must be no "ifs."

The best proof, if such were needed, of the relationship of soundness and conformation in the horse was the view of a horse, hunter, race-horse or draught horse, that had stood up to its work and shown consistent ability over a number of years. Such an animal demonstrated without doubt that its almost faultless conformation with the resulting more true action had enabled the bodily tissues to perform their work with greater ease and less fatigue and so withstand the wear and tear and excessive strains to which they had been put. The less well made not only were unable to work with the same facility, and consequently showed proportionately less ability, not even the full ability of which they might be possessed, but might early become unsound and unfit for work. Of what merit would it be, asked the speaker, to have an animal possessed of high intrinsic ability if it were unable to stand up to the work necessary to display it? It was upon seeing one of the well-made, proved animals that one might well exclaim, "What conformation, what balance, what presence!"

The General Discussion

Mr. F. G. Waddington (Watton, Norfolk) said: "I notice that Mr. Dawes and Mr. Brayley Reynolds have different opinions on one point; that is the advantage of a horizontal croup in relation to the development of speed. From my experience of my friend Mr. Dawes I have no doubt that he will be able to support his own opinion very ably but I thought it might help him if we considered a little comparative anatomy.

"The fastest animal in the world is the cheetah and those who have seen a cheetah in action will know that its croup is quite horizontal. On the other hand, the elephant—enormously strong and able to shift great weights—which is a relatively slow moving animal, has its croup approaching the vertical. Again, if we consider *Homo sapiens*, a human athlete who wishes to make a strong, fast start to a race, crouches down so that his pelvis is more horizontal, to give him a better thrust with his legs.

"I think that speed is dependent on a long, sweeping stride with the hind legs, and this is governed by the extent to which the femur can move in relation to the pelvis. It seems to me that greater movement, and the consequent longer stride, must be favoured by a more horizontal pelvis."

Mr. Wm. C. Miller (Newmarket) said: "I should like to add my appreciation of the excellence of the paper by Mr. Dawes and of the opening of the discussion by Mr. Reynolds. There is much satisfaction to us to know that interest in the horse is still so well maintained, even though opportunities for building up the individual experience and knowledge of the horse by the average veterinary surgeon to-day

cannot be so great as they were years ago. It is a privilege to hear the results of so much experience so clearly discussed. Instead of the dogmatic statements of the older authors we have had many reasons given for the views held. But I still have a minor quarrel with both authors in that I personally would have liked to have heard even more reasons for deciding that this or that type of conformation is the best. To enable an assessment to be made, I think more attention should be paid to what can be called functional anatomy. Perhaps the question of a flat or a sloping croup could be better appreciated, if for each type an argument based upon the functioning of the muscles of propulsion were included.

"The other comment is that I have always felt that it is very difficult to give the right emphasis to one or another particular fault or merit of conformation in relation to others. If a riding horse has particularly good shoulders and fore limbs, and poor, weak hocks, second thighs and buttocks, is it a better or a worse horse than the one which has an excellent hind end and is poor in front? In the really superior horses which have 'balance' and 'presence' the difficulty does not arise, but how many more of the other sort do we see.

"Finally, the two papers are extremely valuable and are the results of lifetimes of experience. I hope that someday both authors may be persuaded to put more of their experience on paper for the benefit of those who now can never have the same chance to build up their own experience and knowledge in the same way. We must always remember that in the world as a whole there are many countries where the horse is still of great importance, even though in Britain we are seeing the inevitable decline of the horse population brought about by mechanisation of haulage and transport. May I personally thank both contributors very much indeed for their stimulating papers."

The Reply

Mr. Dawes, replying to the discusssion, said that he was very gratified by the response to his paper, in that it had provoked not only a first-class discussion but also a great amount of interest from a large number of people.

He was indebted to Mr. Brayley Reynolds, not only for the leniency of his attitude towards the paper but also for opening the discussion. There was little difference between them when it came to the point. Only one real argument had arisen. Mr. Brayley Reynolds had said, quite right that horses were either sound or unsound. Many horses which were bad from the point of view of conformation and which were likely to perform badly in the future were often at the time of examination technically sound and these horses constituted a headache for the experienced examiner. If a horse was "made right" and if its conformation was reasonably correct, it would prove most likely to be a sound horse. He had proved that repeatedly.

He had seen on many occasions thirty or forty cobs from mid Wales which, apart from colour and marking, were all extremely alike. They all had a short back, were low to the ground, on the best legs and feet, and were all of the same mould.

One had to keep in mind a picture of the presence, balance or type, whatever one liked to call it, for which one should look in a horse. Conformation was of the greatest value in the selection of horses. Nothing sharpened perception more than the experience of having to spend £1,000 of other people's money on buying horses. He thought that "presence" was an all-important factor, but if Mr. Brayley Reynolds preferred the word "balance" they would not quarrel over that.

Reference had been made to the long, lean neck. In writing the paper he was thinking not of the attenuated neck that was unpleasant to look at but of the neck which was free from undue "crestiness" and which gave the animal a good rein. "Crestiness" was often associated with shortness of neck and the animal that had that often "died" away after a short while, was never satisfactory and never went into its bridle as it should do.

The opener of the general discussion wondered whether girth measurement had anything to do with the heart and the respiratory organs. This was a point on which the speaker was adamant and dogmatic because he believed that a horse with a deficient girth measurement was never likely to be strong constitutionally.

Girth measurement had something to do with the functioning efficiency of the heart and lungs. In the case of a horse like Mighty Atom the operative description was "big," and such animals had the girth that was necessary if they were to remain sound in wind and heart. Nevertheless, it was the big horse which presented a special headache for the examiner, because so many big horses were unsound in wind. He had yet to be convinced of the chief predisposing cause of the big, well-made horse becoming unsound in wind.

Reference had been made to the fact that he had not stressed that the young horse which was put to work too early was inclined to develop roach back. The opener had said that he had met the same trouble in two-year-olds of the Thoroughbred class. If a two-year-old pony had to carry a sturdy child it might have some alteration of the spinal column years later. Roach-backed horses seldom lay down and they usually became shiverers eventually. He did not consider that shivering was as prevalent as it used to be, but an artificial impression to the contrary had possibly been caused by the reduction in the number of horses.

He was glad that on the question of the straight croup the opinion of the meeting was about fifty-fifty. He had found the tendency towards a straight croup most marked in many horses. A high proportion of good show jumpers that he had seen, particularly ten or fifteen years ago, had been straight crouped. It might be said that the opener of the discussion had referred in this connexion not to show jumpers but to race-horses. In the speaker's opinion the straight crouped horse had a better conformation.

Mr. Brayley Reynolds had done a great service by emphasising the danger of a deviation, inward or outward, of the knee itself. The knee was probably the most important joint in the body. It certainly took the greatest stress. The horse with calf knee had shockingly bad conformation. There had appeared in *Sporting Life* a picture of Merry Deal going over the last flight to win the Champion Hurdle race this year. The photograph was an education in the amount of over-extension of the knee that could take place and was a striking example of the stress to which the knee could, for a fraction of a second, be put. One could understand what over-extension entailed when applied to a calf knee; the ligaments were bound to be torn or damaged.

The speaker said his experience of Thoroughbred horses was largely concerned with those running under National Hunt rules. Injury to the knee might be a cause of enormous wastage in the Thoroughbred horse. Once the knee started to give trouble, a horse's racing days were likely to come to an end. As soon as a marked periostitis of the knee occurred, it was likely that the horse would not be able to stand up to further training.

Professor Mitchell had probably given the answer to the question why the hind legs did not suffer as much as the fore legs. The addition of the head and neck to the body was closely associated with the work done by the fore legs and at all times there was greater stress on the fore legs than there was on the hind legs. Compared with the hind legs, there was greater mobility in the fore legs and greater masses of muscle associated with them.

Mr. Shuttleworth had expressed the hope that some of the best horses, such as Hackneys, would not develop into purely show animals. The butcher, baker or candlestick maker no longer delighted in using a good horse when delivering his goods. It was perhaps better for the commercial horse to go rather than to descend in the social scale because of the difficulty in finding anyone to drive him. There was no doubt that the disappearance of the commercial horse had been accelerated by the scarcity of people to drive.

The observations of one contributor to the discussion could be summed up in the words, "Don't buy a horse that you don't like." If a buyer trusted his hunch, he was not likely to go far wrong. The acid test as to whether a purchase had been a good one was, "Did you like the horse better after you had taken it home than when you bought it?" If a purchaser felt pleased with the horse when he had taken it home, there was not much wrong with it.

He did not agree entirely with what had been said about the length of the pastern. Some animals had a straight

hock and sloping pastern and when they moved the fetlock descended almost to the ground. That was very bad formation. He sometimes wondered when looking at a foot what was the significance of level rings. While uneven rings indicated a certain condition, there were some formations which were nutritional conditions only. They were produced entirely by changes in nutrition, and it was likely that sooner or later, with proper shoeing attention, they would disappear. He disliked the irregular ring, as it indicated some sub-acute inflammatory condition of the foot.

Lameness might occur in a good many instances before the clinical pattern was manifested. He knew of nothing more difficult in that respect than the horse which was developing some arthritis of the hock. It would exhibit lamenes to some degree before the cause could be pinpointed. Lameness sometimes occurred long before any clinical explanation became apparent.

Major Carey-Foster had referred to the straight croup and, while not agreeing with the author of the paper, brought up a very interesting point and stressed the value of a certain length of the neck and the importance of distance between hip and hock.

Mr. Miller, who had induced the author to write his paper, had asked for reasons for some of the views expressed therein. If he were to sit down and consider, he might be able to give more reasons, but he was unable to do so at the moment. Among horsemen, including veterinary surgeons, there were nearly always reasons for implicit beliefs.

As to the difference between conformation and beauty, he believed that good conformation was beauty, although "beauty" was a word that he did not like to hear applied frequently to animals, as it reminded him of a Pekingese in a satin-lined basket. However, a well-made horse was a beautiful animal. A horse could hardly be beautiful unless it were put together properly, and a horse that was put together properly did not often have very much the matter with it.

Mr. Dawes said that he had a theory that some courses were more likely to cause a breakdown in a horse than were others. Sometimes when a horse was to be sent to a particular meeting he advised the owner against doing so because the course was, in his opinion, unlucky. There might be something about it that led to strained tendons.

Mr. Runciman had rightly stressed that the be-all and end-all of conformation in a horse was the good foot. The majority of troubles in the horse arose from defective feet. He disliked seeing an odd-footed horse. The man who was examining horses day after day learned to attach great importance to odd feet. One was sometimes told that an animal was born with odd feet, but more often than not the condition was indicative of disease.

A Study of the Treatment of Inoperable Malignant Tumours in Dogs

BY

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THIS paper is an account of the beginning of a collaborative study of the treatment of inoperable malignant tumours in dogs made possible by the establishment of the School of Veterinary Medicine in Cambridge.

In human medicine, the methods to be considered in the treatment of malignant tumours are surgery, radiotherapy and in recent years, chemotherapy, in this order. Surgery and radiotherapy alone or in combination are used in both radical treatment, aiming at permanent healing, and in palliative treatment. Radiotherapy is the only agent, apart from surgery, which has cured substantial numbers of patients with malignant tumours, but is also of great palliative value. Chemotherapy is being developed intensively. At present it is mainly used in palliative treatment, and apart from hormone therapy is almost invariably of much greater value for leukaemias, lymphomas and some highly anaplastic tumours than for the common cancers. However, most of the beneficial effects of chemotherapy are only temporary.

The aims of this study are two-fold.

1. To try to develop practical methods of non-surgical treatment of malignant tumours in dogs by means of radiotherapy and also, if possible, chemotherapy, and to extend the use of radiotherapy in this field, where suitable facilities are available, and

2. To gain information of value in the treatment of neoplastic and allied diseases in man. One extremely important advantage is that the tumours in dogs are spontaneous tumours.

Malignant tumours in dogs are relatively common and they have been studied—especially from the point of view of patnology—by many workers, including Feldman (1932), Willis (1948), Mulligan (1949), Cotchin (1954, 1956b). There is obvious need for further study in this country of the non-surgical methods of treatment of neoplastic and allied diseases in dogs. Mr. G. C. Knight, of the Royal Veterinary College, London, has used radiotherapy in the treatment of a number of dogs with malignant tumours (see Cotchin, 1956a). In the field of chemotherapy in a pioneer paper Innes, Parry and Berger (1946) (see also Parry & Innes, 1947) described the treatment of a case of acute lymphatic leukaemia in a dog by means of urethane.

There are many reports from Europe and North America of the use of radiotherapy in dogs, but these include only limited evidence on the results of treatment of malignant tumours (Emmerson, 1949; Pommer, 1950; Thom, 1950; Germain, 1952; McClelland, 1952; Bodingbauer, 1954). Skin reactions to X-rays have been studied in some detail. Pommer and Mähling (1931) showed that among other changes, the epilation dose for 120 kVp X-rays filtered with 1 mm. aluminium was between 780 and 960r for the normal hairy skin of the dog and between 420 and 600r for the hair growing in shaved skin; the human epilation dose for the same radiation was given as 480r (see also Hronovsky, 1925). Thom (1950) stated that dog skin is relatively less sensitive to radiation than human skin, and suggested that safe human skin doses of X-rays could be multiplied by 1.8 and applied safely to animals. McClelland (1955) quoted this as a useful figure but then gave a number of observations of the effects of various doses of X-rays on the skin of different animals, which suggest that there is at least as much individual variation in skin sensitivity to radiation in dogs as in man.

Although stilboestrol is commonly used to check the growth of adenoma of the circum-anal glands in male dogs (Smythe, 1945, 1946), this condition is very responsive to X-ray therapy (Thom, 1950; McClelland, 1955). Hormone treatment of mammary tumours in the dog was described by Ojemann (1945).

In the field of chemotherapy, a few investigations of tumours in dogs have been made over many years. Exner and Sywek (1905) studied cholin. Sticker (1908, 1911) used arsphenamine, atoxyl and arsenite. Neuberg and Caspari (1912) and Neuberg, Caspari and Löne (1912) tried derivatives of antimony and copper. A number of French workers (Dumathras, 1934; Ousmane, 1936; and Bobeau, 1938) studied snake venoms. Strong and Whitney (1938) tried heptaldehyde. McClelland (1947) treated the so-called round-cell sarcoma of the skin of the dog successfully with repeated injections of neoarsphenamine. Following the use of urethane by Innes, Parry and Berger (1946), several other compounds have been studied in the treatment of lymphatic leukaemia in dogs. Englert and Göbel (1954) used nitrogen mustard. Mastrangelo and Barth (1954) reported clinical recovery, which lasted for at least five years, after treatment with nicotylamide (pyridine-3-carboxylic acid amide). The toxic effects of 6-mercaptopurine and related compounds of therapeutic interest have been studied in dogs (Philips, Sternberg, Hamilton & Clarke, 1954) but in contrast with these results, it must be mentioned that there were no signs of impaired liver function in patients treated with 6-mercaptopurine (Burchenal, 1954).

Clinical Material

Since November 1955, up to April 30th, 1957, 7 dogs with a variety of histologically verified inoperable neoplasms have been treated. In 5 cases the condition was definitely malignant; the other 2 cases were of multiple papillomata of the skin, and adenoma of the left vocal cord. The relevant details of each case, including the treatment and subsequent course, are summarised in the Table.

TABLE

Case No.	Breed	Sex	Age years	Site of primary tumour and clinical stage	Histology	Clinical details including extent of tumour	General condition and complicating conditions	Summary of radiotherapy	Subsequent clinical course	Survival: After first sign	Survival: After first treatment	Cause of death
1	French Bulldog	F	7	Carcinoma mammae (left posterior) St. IV.	Adenocarcinoma—poorly differentiated	Left inguinal and abdominal mammary glands. Primary tumour 14 by 4 cm. fungating and extending 3 cm. across mid-line posteriorly. Multiple cutaneous and subcutaneous metastases medial left thigh.	Good. Rapid progression of primary and metastases during oestrus.	Medial and lateral mammary fields and direct inguinal areas S.D.1630r M.T.D. 1500r. Repeated at 4 weeks interval. I–V Synkavit and I–V Compound XIV.	Moist reaction at 5 days after first treatment. At maximum after 10 days. Fungating mass healed after 18 days. All metastases partially retrogressed.	3 months	4 weeks	Probably cerebral haemorrhage during anaesthetic. Also rupture of ileum at site of one of peritoneal metastases.
2	Spaniel	F	10	Multiple papillomata—skin, anterior left carpus—inoperable.	Papilloma	Treated lesion: 7·5 by 4·5 cm. maximum thickness 3 cm.	Obese and sluggish.	Medial and latera fields S.D. 1470r M.T.D. 1500r.	Epilation beginning after 10 days. Rapid retrogression of mass. Almost complete disappearance after 3 weeks.	1 year	6 months	Destroyed—senility.
3	Cairn Terrier	M	11	Adenoma—larynx—left vocal cord.	Adenoma	Rounded nodule 5 mm. diameter on left vocal cord.	Respiratory embarrassment and stridor. Obese and cyanosed. Encrusted teeth.	Rt. and Lt. lateral fields 5 by 5 cm. 8 cm. separation. Unit S.D. 860r M.T.D. 800r. Repeated after 30 days.	No skin reaction seen. Lesion disappeared — almost completely before second treatment.	10 months	6 months	Destroyed—senility.
4	Newfoundland	M	7	Tumour mouth—upper jaw opposite left carnassial tooth invading palate and lip. Mobile L. submaxillary gland. St. III.	Sarcoma — A pleomorphic cell malignant tumour invading muscle.	Excised but recurred to original size in 7 days.	General condition good. Slowly losing weight.	Direct field to primary 5 cm. dia. circle S.D.1500r and 4 weeks later 12·5 cm. dia. field to submandibular area S.D. 1500r.	Primary disappeared after treatment but secondary glands continued to grow and were removed in block dissection. Rapid recurrence after surgery. Post-operative I–V compound 40, and later 14. All but one metastatic gland retrogressed during administration of Compound 40.	12 weeks	10 weeks	Destroyed-discomfort and multiple metastases, lymph nodes and lungs.

5	Cross-bred ? Alsatian	M	4	Lymphadenoma—generalised. Sr. IV.	Lymphadenoma (Hodgkin's disease).	Generalised involvement of superficial lymph nodes, liver, spleen and bone marrow.	General condition good. Rather obese. Fluctuating fever.	—	I.V. Nitrogen mustard oxide therapy. Glands started to soften after 3 days.	5 weeks	4 days	Sudden death about 5 hours after 4th injection of 100 mg. nitrogen mustard oxide. Lungs congested and consolidated. Acute pancreatitis. All lymphoid tissue haemorrhagic.
6	Alsatian	M	6½	Acute leukaemia. St. IV.	Probably lymphoblastic.	Generalised enlargement of all lymph nodes. liver and spleen. Marrow involved.	General conditions very poor. Apparently moribund.	—	I.V. Nitrogen mustard oxide therapy. Dramatic improvement after 3 days. 2 short episodes of diarrhoea during treatment.	6 weeks	3 weeks	Destroyed *in extremis*. Coma and collapse with generalised purpura. 3 days after last injection of 50 mg. of nitrogen mustard oxide. At *P.M.* extensive haemorrhages and gross enlargement of all lymphatic tissue.
7	Airedale	M	8	Carcinoma — Rt. tonsil, mobile Rt. tonsillar gland. St. III.	Squamous carcinoma.	Primary 2 by 1·5 cm. Gland 3 by 2·5 cm. and very hard.	General condition good but losing hair. Painful throat.	Intra-oral field 3·5 cm. dia. Applied dose 1590r. Opposing tonsillar field 5 by 5 cm. S.D. 1470r. M.T.D. 1500r.	Primary regressed completely in 18 days and lymph node returned to normal size. Pain in throat persisted with some laryngitis. At almost 6 weeks infectious pharyngitis controlled with Sulphamezathine. Then 4 weeks later Rt. parotid region became swollen and after a further week the Rt. prescapular gland was large and hard.	13 weeks	11 weeks	Destroyed because of continuing pain. *P.M.* large tumour mass in parotid. Primary site showed recurrence, but treated tonsillar gland showed no evidence of tumour. (No cartilage necrosis). Metastases L. anterior mediastinal nodes.

Radiotherapy

In general, the aim is usually radical treatment; palliative treatment seems permissible in veterinary medicine only when it gives relief from pain or discomfort in an animal that is otherwise apparently healthy. Most owners of dogs are not prepared to keep animals that need much nursing, and economic factors are important with large dogs.

It is impracticable in the case of dogs to use the technique most commonly employed in human radiotherapy of fractionated X-ray doses repeated daily on week-days for 3 to 6 weeks. Apart from the question of hospital kennel space, in general it is not possible to ensure that the dog is immobilised during treatment unless it is anaesthetised. It is not possible with dogs to use the method devised for rats which employs a flexible lead plate with a hole for the tumour (Mitchell, 1955). Repeated daily anaesthetics are obviously impossible particularly in old animals—and most of the dogs with tumours are old. With repeated anaestnetics the risk in such animals of anaesthetic death or pneumonia becomes greater than that from the tumour. It must be emphasised that the dog cannot be held by an assistant during treatment on account of the radiation hazard.

Accordingly, it is necessary to compromise in deciding upon the general plan for radiotherapy in dogs. In human medicine, single-dose radical treatment is sometimes valuable in elderly patients with small radio-curable lesions, but this method of treatment is not generally applicable because it appears to be liable to a higher incidence of late recurrences after many years than fractionated treatment. With single dose treatment or relatively few fractions, the differential radiosensitivity of the cells of the tumour in relation to those of the normal tissue is usually reduced and, further, the volume of tissue which can tolerate radical irradiation appears to be less. For some radiocurable human tumours such as squamous carcinoma of the lip, excellent results are obtained by using 7 fractions of the X-ray treatment in over-all time 8 days. However, such treatment is limited in its indications and scope. It must be emphasised that in human radiotherapy, despite the vast number of investigations and studies, there is still far too little known about the effects of fractionation to decide with confidence upon the most efficient method of fractionation and the optimal over-all time of treatment for individual tumours. A short over-all time such as 8 or 16 days has the advantage that the radiation is delivered before the normal tissue reaction starts. There is clinical evidence that the radiosensitivity of the normal tissues increases during the reaction stage but it is uncertain how the tumour behaves in this respect. On the other hand, the long over-all times have the advantage that it is possible to control the course of the treatment by repeated clinical observation; and in general, as a matter of experience, the best results are often obtained using long over-all times.

Accordingly, in radiotherapy in dogs, some treatments have been carried out with single doses (which includes the use of multiple fields at the same visit) and in other cases two doses were used at an interval of about 4 weeks. Probably the best compromise plan of treatment would be to give 4 treatments in over-all time 9 days so that there is an interval of 2 days without treatment between each fraction.

Many different techniques have been described (*e.g.*, Thom, 1950). The technique used by Knight for X-ray therapy of accessible tumours in the dog has been described by Cotchin (1956a) "The apparatus used has a 200 kV peak at 8 mA. Depending on the lesion, the total dosage has varied from about 1,500 to over 3,000r. In general, the plan has been to give an initial dose, calculated at the surface of the lesion, of 200 to 400r, followed by increases of 100r, and increasing intervals in days, *e.g.*, an initial dose of 200r, followed by 300r after a one-day interval, 400r after a two-day interval and so on. The kilovoltage used has been from 100 to 160." For the radiotherapy of circum-anal adenoma, McClelland (1955) considered that the optimal surface dose was 3,000r, given in 10 fractions, each of 300r, at approximately weekly intervals. Thom (1950) recommended doses of 320r weekly to a total of 2,500r.

In the veterinary applications of radiotherapy, it is important to make use of the extensive experience and practice of human clinical radiotherapy. A valuable book of reference for this purpose is the *British Practice in Radiotherapy* (1955). Quite apart from clinical experience and radiobiological knowledge, radiotherapy requires the applications of physical methods and the knowledge and experience of a hospital physicist.

It is regrettable that there has always been a tendency in reports on veterinary radiotherapy to refer only to skin dosage. In addition it is essential to calculate, and sometimes also measure, the dose distribution throughout the whole volume of irradiated tissue and prescribe in terms of the minimum tumour dose (M.T.D.) appropriate to the given irradiated volume and time factors, of which the most important are the over-all time and method of fractionation. In planning the treatment it is often necessary to evaluate the dose at normal organs and tissues which may show serious late degenerative changes, *e.g.*, the kidneys, heart and spinal cord. It is always wise to use sufficiently high energy X-rays and sufficient filtration to avoid excessive additional energy absorption in bone, which is a tissue particularly liable to necrosis.

Technique

The X-ray therapy apparatus used was the Maximar machine, run at 220 kVp, often with added filter of 1 mm. aluminium (H.V.L. 0.4 mm. copper; effective wavelength 0.25A) as in Cases 1, 2 and 7. Where greater penetration was required or the treatment involved irradiation of bone or cartilage, the added filter used was either 1 mm. copper plus 1 mm. aluminium (H.V.L. 1.5 mm. copper; effective wavelength 0.12A) as in Case No. 3, or 2 mm. copper plus 1 mm. aluminium (H.V.L. 2.0 mm. copper; effective wavelength 0.115A) as in Case No. 4. The usual types of applicator were employed with F.S.D. 35, 40 or 50 cm. The dose rates were checked with measurements in phantoms when necessary.

The simplest standard techniques of human radiotherapy have been used. These have employed either a single field or two opposing fields with Perspex formers for linear alignment. Bolus bags are used to secure full backscatter. For evaluation of depth dose distributions, standard methods of calculation or phantom measurements have been used. Absorption by intratracheal tubes must be allowed for in some cases; absorption by hair is usually allowed for by measurement of distances from the end of the applicator which is applied with compression.

Assessment of Case

(1) *General condition*

Account must be taken of any condition which is likely to increase anaesthetic risks. It is, however, interesting that dogs with malignant tumours, other than those which prevent eating due to pain or obstruction and the leukaemias, appear to remain in good condition even when there are extensive metastases.

Anaemia may be an important complication of malignant disease, and if at all severe will reduce the response of the tumours to radiotherapy on account of the low oxygen tension in the tissues. Blood transfusion may be indicated if there is a severe anaemia. In human medicine, anaemic patients are now usually transfused before radiotherapy.

(2) *Stage of advancement of tumour*

For many years the importance of defining the stage of advancement of malignant tumours has been recognised in human medicine. The internationally agreed staging of carcinoma of the uterus has proved of great value in assessment of the results of treatment as shown in the Annual Reports published in Stockholm.

The W.H.O. Expert Committee on Health Statistics (W.H.O. Technical Report Series No. 53) laid down principles for the staging of malignant tumours in accessible sites. Adoption of these principles in veterinary medicine would help in planning treatment and in prognosis.

The principles of staging are as follows:—

Stage I. Tumour confined to the organ and of relatively small size.

Stage II. Tumour limited to the organ of origin but of relatively large size, or with limited extension beyond the original organ.

Stage III. Tumour with wide infiltration reaching neighbouring organs.

Stage IV. Tumour with considerable involvement of adjacent tissues or having spread to neighbouring organs.

For some sites the use of a second or supplementary system might be of advantage to describe direct or metastatic involvement of the lymphatic system or of other organs.

The stage of each case should be decided at examination prior to treatment.

It was considered that the use of a "Stage O" which appears as a pre-stage sometimes developing into cancer, should be reserved for cases not considered to be invasive and that in the presentation of therapeutic statistics, this category should be kept apart from Stages I to IV.

(3) *Histology*

Histological examination of a biopsy or surgical specimen is essential both for diagnosis and for planning treatment. It has been said that there are differences in the malignancy of human and animal tumours of comparable histology, but it is dangerous to generalise in this way. We have used the classical criteria of human histopathology and have found no serious disagreement with the clinical behaviour of the tumour in the very limited number of cases under consideration.

In view of the discussions concerning the nature of the condition in dogs resembling Hodgkin's disease (*cf.* Willis, 1948, p. 780; Stalker, Schlotthauer & Feldman, 1936; Barchfield, 1953) it may be of interest to mention that Case 5 in the Table showed a histological picture indistinguishable from that of Hodgkin's disease in man.

Anaesthesia

Anaesthesia has been by induction with pentothal after medication with omnopon and scopolamine, morphine or largactil, followed by gas, trilene and oxygen or fluothane and oxygen. Nembutal has been avoided because there is some evidence that it may reduce radiation response.

In one animal anaesthetised with pentothal after morphine premedication, there was a serious deepening of anaesthesia during the intravenous administration of a radiosensitising drug, Compound XIV (see below), 100 mg. per 12 kg., prior to irradiation. This effect may have been due to potentiation of the anaesthetic or may have been an individual idiosyncrasy; it was not observed in another dog.

Radiosensitisers

Certain substances, of which the simplest is oxygen, increase the radiosensitivity of cells and under suitable conditions increase the differential therapeutic response of tumours. (This is an extensive subject; for information on oxygen effect see Gray, Conger, Ebert, Hornsey & Scott, 1953, and on chemical radiosensitisers see Mitchell, 1953, 1955, 1957.)

The oxygen tension of most tissues can be raised by allowing the animal to breathe oxygen at atmospheric pressure instead of air for a few minutes before and during the irradiation (Cater, Phillips & Silver, 1957a, b, c). This procedure was used in all the irradiated cases in the Table.

Use has also been made in two of the cases of the chemical radiosensitiser Synkavit (Compound I, tetrasodium 2-methyl-1:4-naphthohydroquinone diphosphate) and Compound XIV (tetra-sodium 2:3:6-trimethylhydroquinone diphosphate).

After-treatment and Nursing

Following radiotherapy little attention is needed except when certain special regions have been treated. Laryngeal irradiation may be followed after a few hours by oedema of the larynx, which may be sufficiently severe to cause respiratory distress. This is probably less likely to occur if fractional dosage is employed. We have irradiated the larynx region of 2 dogs—one with laryngeal adenoma to central dose 8oor, and one with carcinoma of tonsil to M.T.D.

1,500r, but in neither case was there any subsequent laryngeal obstruction.

Treatment of mammary or abdominal tumours will inevitably result in some irradiation of the alimentary tract, and this may lead to the onset of diarrhoea of short duration. If large areas have been irradiated there is the more serious danger of destruction of bone marrow with its resulting anaemia.

Treatment of the skin reaction consists chiefly of trying to keep the irradiated region dry and, if possible, preventing the animal from licking it.

Hair Loss

It is well recognised that hair follicles are very radiosensitive structures and it is clear that there is a striking individual variation between animals in their susceptibility to epilation.

In our limited clinical material, for the present conditions of irradiation, there was no evidence to suggest that the skin of the dog differed appreciably in radiosensitivity from human skin.

Although permanent hair loss is a small price to pay for the healing of a malignant tumour, an animal with extensive epilation may become very unattractive (Plate I). For this reason it is essential that X-ray therapy should be carried out in such a way as to reduce the possibility of permanent epilation to a minimum. In this series temporary epilation occurred in 3 of the 5 animals irradiated (Cases 1, 2, and 4); there was no epilation in the other 2 animals.

Chemotherapy

We have used 3 compounds as possible chemotherapeutic agents:—

(a) nitrogen mustard oxide (Mitomen) introduced by Yoshida (see Ishidate *et al.*, 1951; see Druckrey, 1956);

(b) tetra-sodium 2:5-dimethylhydroquinone diphosphate, Compound XL in the series of compounds studied (Mitchell, 1955, 1957), and

(c) tetra-sodium 2:3:6-trimethylhydroquinone diphosphate, Compound XIV.

We have treated 2 dogs with nitrogen mustard oxide, one with Hodgkin's disease (Case 5, Table) and one with acute lymphoblastic leukaemia (Case 6, Table). In Case 5 it seems that the dose may have been too high, as the animal died suddenly on the fourth day of treatment and at autopsy showed multiple haemorrhages in the lymph nodes. The dosage was deliberately high (100 mg. per 32 kg.), as calculated on a bodyweight basis from human dosage, since it was hoped to be able to give the treatment over a few days only.

The second case treated with this drug (Case 6) was a dog with acute lymphoblastic leukaemia which was obviously dying. After 4 days' treatment with Mitomen, at a low dosage, 25 mg. per 29 kg., there was a dramatic improvement in the patient, which continued over about 2 weeks, when treatment was stopped owing to lack of further supplies of the drug. Diarrhoea developed twice during treatment, but stopped in each case after 24 hours. When discharged the animal appeared normal and had improved greatly in condition, but after a further 3 days without treatment it collapsed suddenly with multiple haemorrhages and was destroyed *in extremis*. There was evidence of prolonged clotting time and bleeding time as the treatment continued. At the time of death no megakaryocytes were seen in the bone marrow smears. The blood picture was checked daily and is shown in Fig. 1. Abnormal cells at first were greatly reduced during treatment, but later increased. This case is interesting in that the nitrogen mustard oxide does not appear to cause the nausea which often accompanies treatment with other nitrogen mustard derivatives. (This is similar to its effect in man.) It seems that in the dog the megakaryocytes may be more susceptible to its action than in man.

Compound XL and Compound XIV have been used in an attempt to control secondary deposits in lymph nodes arising from an anaplastic tumour of the upper jaw (Case 4, Table). These secondaries had already proved to be relatively radioresistant and had recurred after radiotherapy and surgery, and were growing rapidly. During 6 days of daily intravenous injections of Compound XL, increasing from 100 mg. to 500 mg. daily per 54 kg., the growth of all palpable tumours except one was arrested and tumour retrogression occurred, but growth restarted when the drug was stopped and Compound XIV, 100 mg. intravenously daily, substituted. There was evidence at first of uneasiness following injection of Compound XL, which is consistent with the focal pain in tumours experienced by human patients on many drugs of this series. The histological appearances of the metastatic deposits before and after the retrogression following treatment with Compound XL are shown in Plate II.

It is important to note that Compound XL does not produce retrogression of the transplanted Walker carcinoma 256 in the rat.

Assessment of the Results

This may be done by collecting the following information:—

1. Survival after the first sign of tumour.

This depends chiefly on the observation of the owner, since a slowly growing tumour may not be noticed until it is endangering some vital function.

2. Survival after the first treatment.

This is perhaps the best objective criterion for quantitative assessment of the results of treatment. There is no generally accepted period of survival after treatment of malignant tumours of dogs which is comparable with the 5-year period in human medicine. Owing to the short life span of dogs survival after treatment for about 1 year, provided that the animal was living a normal life, would be very satisfactory. Further, most dogs with tumours are old, and may well be destroyed for reasons other than recurrences of growth, *e.g.*, see Cases 2 and 3 (Table). In Stage IV tumours survival statistics do not reflect the value or otherwise of X-ray treatment in producing palliation.

3. General clinical course after treatment.

Successful treatment of animals requires that there should be no need for prolonged expert nursing,

CHANGES IN BLOOD PICTURE OF A DOG WITH ACUTE LYMPHOBLASTIC LEUKAEMIA DURING & AFTER ADMINSTRATION OF NITROGEN MUSTARD OXIDE (MITOMEN) ONCE DAILY I.V.

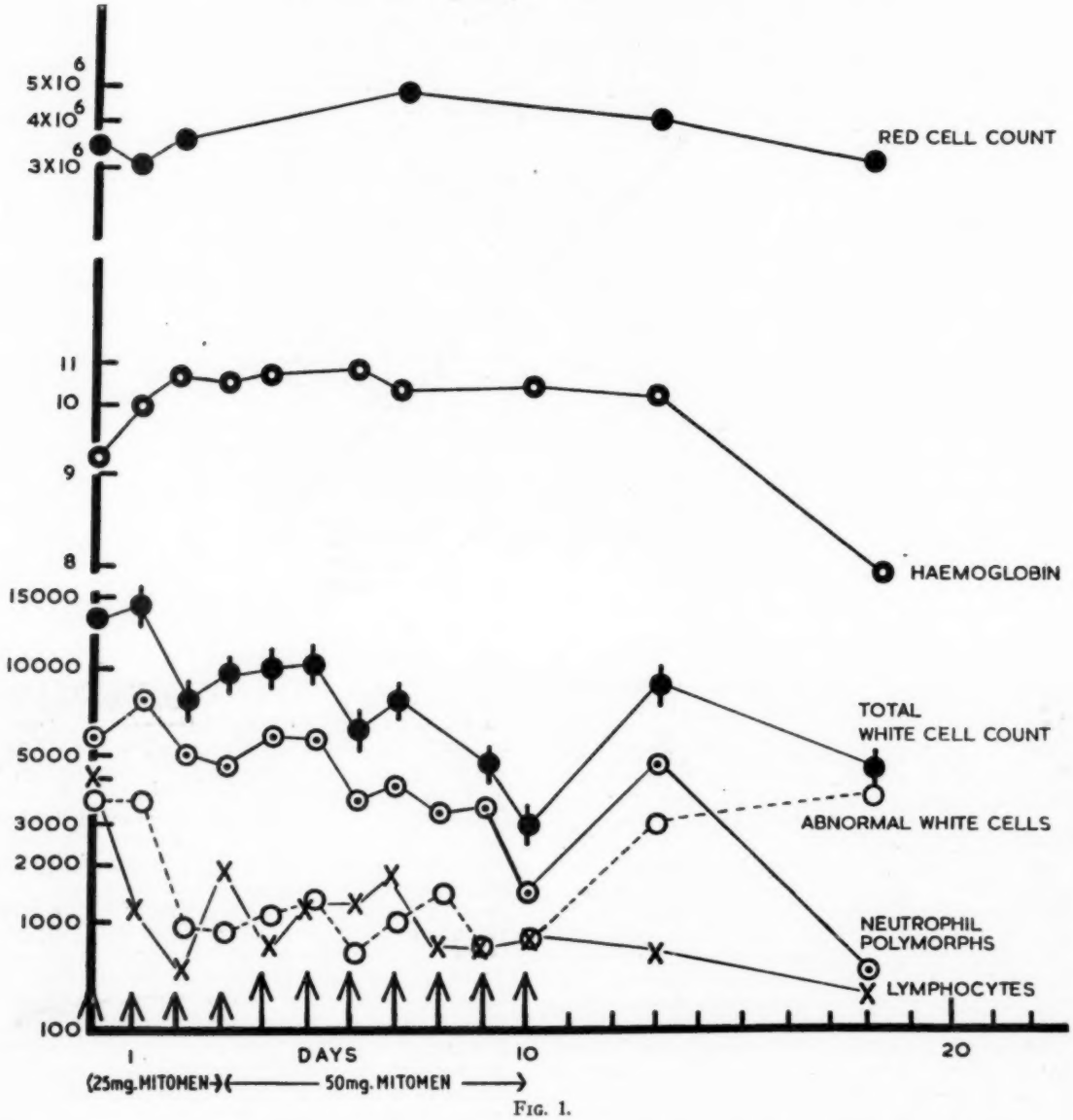

FIG. 1.

both for economic reasons and because it is only the rather exceptional owner who is prepared to nurse a sick dog for more than a few days without becoming discouraged and asking for the animal to be destroyed. The question of hair loss and skin reaction has already been mentioned and is very relevant to the assessment of the results of treatment of the individual animal.

4. Cause of death.

Where possible, a full *post-mortem* examination should always be carried out, otherwise much valuable information may be lost which could usefully be applied to later cases. This is especially relevant when methods of treatment are being investigated.

Of the 7 cases in the Table, the 5 which had genuinely malignant tumours died or were destroyed for reasons connected with their tumours but the other two were destroyed because of old age and showed no evidence of persistent tumour.

J. S MITCHELL & I. A. SILVER.—A STUDY OF THE TREATMENT OF INOPERABLE MALIGNANT TUMOURS IN DOGS

PLATE I.—EPILATION AFTER X-RAY TREATMENT OF MAMMARY CARCINOMA AND SKIN METASTASES.

FIG. 1.—Two weeks before treatment.

FIG. 2.—Twelve days after irradiation; early skin reaction.

FIG. 3.—Twenty one days after irradiation; extensive hair loss.

PLATE II.—HISTOLOGICAL APPEARANCES OF RECURRENT METASTASES IN LYMPH DOSES OF ANAPLASTIC SARCOMA OF MOUTH (CASE 4) BEFORE AND AFTER RETROGRESSION FOLLOWING TREATMENT BY MEANS OF INTRAVENOUS INJECTIONS OF TETRA-SODIUM 2:5-DIMETHYL-HYDROQUINONE DIPHOSPHATE (COMPOUND XL).

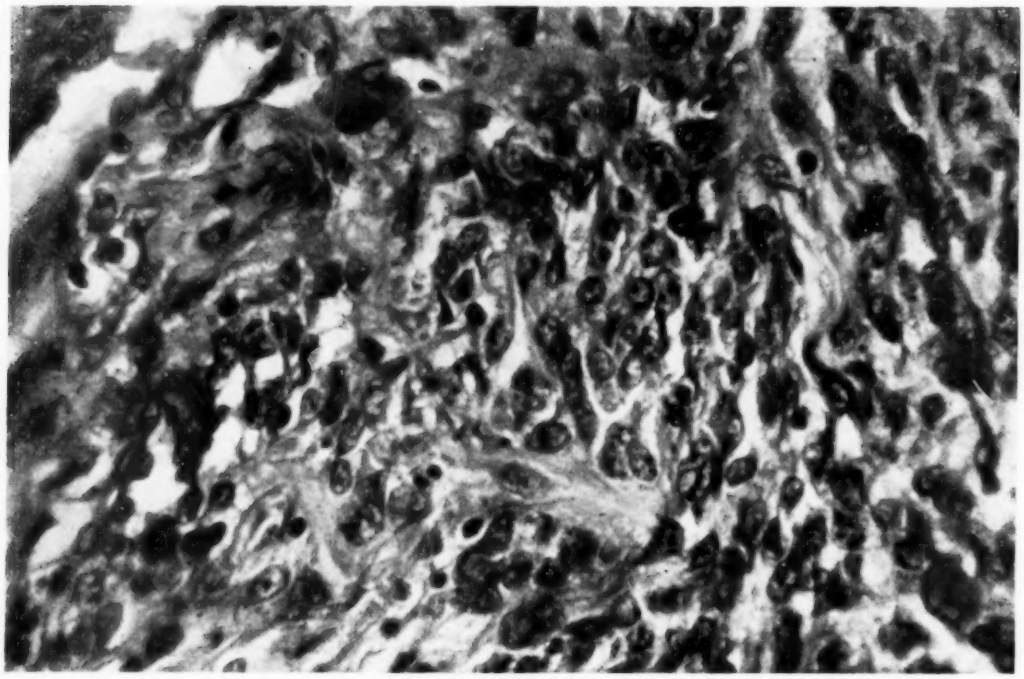

FIG. 1.—Before treatment.

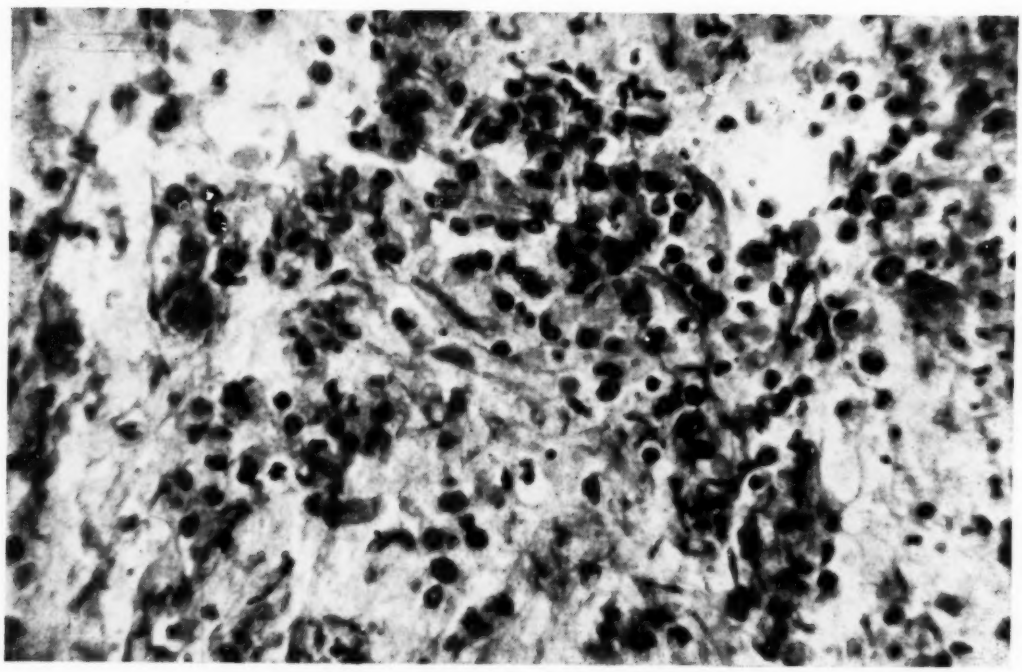

FIG. 2.—After treatment, showing widespread degeneration of the tumour.

Other Investigations

Useful information has been obtained by means of electrode potential studies using the methods of Cater, Phillips and Silver (1957a, b, c). Before treatment in 3 cases (Nos. 1, 2 and 5, Table), platinum and gold electrodes were inserted into the tumours and some normal tissues, and measurements made of the oxidation-reduction potential and oxygen tension. These measurements were made primarily to obtain quantitative information concerning the differential uptake of the radiosensitising drugs by the tumour in relation to the normal tissues.

The inhalation of oxygen at atmospheric pressure caused a striking increase in the oxygen tension in both the tumour and normal tissues in the cases examined. These changes observed in the dogs were similar to those seen in human patients.

The potential chemical radiosensitisers, Synkavit (Compound I), and Compound XIV, produced striking falls in oxidation-reduction potential. These studies, and similar measurements on rats with the Walker carcinoma and Jensen sarcoma, showed that after intravenous injection of Synkavit the oxidation-reduction potential of the normal tissues returned to normal values within about 30 minutes, while in the tumour it recovered much more slowly (see Fig. 2).

FALLS OF OXIDATION-REDUCTION POTENTIALS IN MAMMARY TUMOUR OF BITCH, AND NORMAL TISSUE AFTER I.V. INJECTION OF 50 MG 'SYNKAVIT'

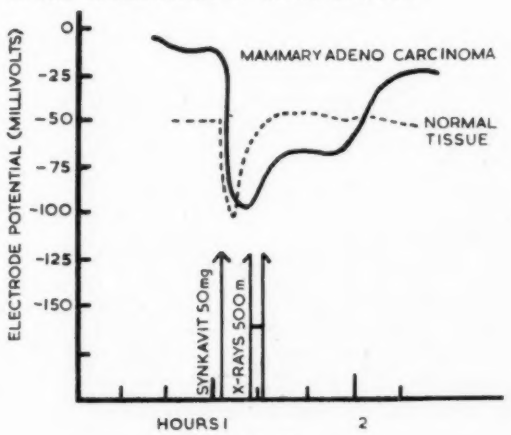

FIG. 2.

For effective radiosensitisation it is essential to irradiate at a time when there is maximum differential effect between the tumour and the adjacent and interwoven normal tissues. It is interesting that the choice of an interval of 30 minutes between the intravenous administration of Synkavit and irradiation which was made empirically is supported by the measurements.

Nitrogen mustard oxide did not affect either the oxidation-reduction potential or the oxygen tension in the lymph nodes of the dog with lymphadenoma (Case 5) during the time of the measurements.

Conclusions from the Present Limited Study

Our own limited experience and the information given in the literature suggest that radiotherapy is a practicable method of treatment of both malignant and non-malignant tumours in dogs when satisfactory equipment and facilities are available. Good results usually depend on the observation of the owner and the diagnosis of the practitioner to ensure early treatment.

In considering the development of deep X-ray therapy in the treatment of malignant tumours in dogs, it is essential to discuss the cost. Using 220 kVp X-ray apparatus, the total cost of a course of treatment to deliver a minimum tumour dose of 2,500 to 3,000r, including depreciation of equipment, but not the salary of technical staff, is about £6.

We hope that there will be further opportunities to develop the scope of the radiotherapy of malignant tumours in dogs. One of the aspects upon which such a study may give information in human medicine is the value of different types of dose fractionation and the question of optimal over-all time of treatment. We also hope that it will be possible to try to treat leukaemias and lymphomata and tumours with generalised metastases in dogs by the method of whole body irradiation followed by bone marrow replacement, which has already been carried out in mice with leukaemia by Barnes, Corp, Loutit and Neal (1956).

The introduction of clinical staging of malignant tumours into veterinary practice is recommended. It is considered to be essential for proper assessment of the results of treatment and highly desirable in making decisions concerning the method of treatment in the individual case. It is suggested that consideration should be given to formulation of methods of staging of malignant tumours with special reference to tumours in animals. It is appreciated that there may well be differences in detail from those evolved for the human diseases.

The use of an agreed staging greatly facilitates the comparison of clinical material in different places and at different times. A related point of interest is that in human medicine there is often a suspicion of a change over the course of years in the natural history of diseases, including malignant tumours. In veterinary medicine it appears that, similarly, mammary tumours in female dogs are becoming more malignant during the last 20 years. This is not the place for detailed discussion of possible causes of this change, but the question may be raised, in view of suspicions in human medicine, as to a possible rôle of the administration of stilboestrol. However, by employment of staging, one can take some note of changing natural history.

It seems likely that most of the malignant tumours seen in dogs at the present time are in Stages III and IV. Accordingly, it is to be expected that the results of any form of treatment will not be very good, though it may prove possible to heal a small proportion of these tumours by means of radiotherapy, quite apart from the question of palliation by radiotherapy. Moreover, extrapolating from human medicine, it is clear that radical surgery is contra-

indicated in most of these cases. It is suggested that in Stage III cases of mammary carcinoma, worse results are likely to be obtained by surgery as the primary treatment than by radiotherapy.

In human medicine, there is a great deal of conflicting evidence concerning the value of pre-operative and of post-operative X-ray therapy, especially in the treatment of mammary carcinoma. It is suggested that information about these problems might be obtained by systematic study of malignant mammary tumours in dogs, particularly in Stage II if a sufficient number of cases were available. In Stage I, the treatment will probably always be surgical.

There is an urgent need to develop effective chemotherapy of cancer in human medicine. In veterinary practice, chemotherapy of malignant tumours would probably become the most acceptable method of treatment. It is clear from our present limited studies that investigation of possible chemotherapeutic agents in the treatment of advanced spontaneous malignant tumours in dogs provides information of great value in human and veterinary medicine.

Summary

This paper describes the beginning of a collaborative investigation of the treatment of inoperable malignant tumours in dogs by means of radiotherapy and chemotherapy. So far, 7 dogs with histologically verified inoperable neoplasms have been treated; in 5 of these, the condition was definitely malignant. Problems of the technique of deep X-ray therapy are discussed. Oxygen inhaled at atmospheric pressure and chemicals, especially Synkavit, have been used as radiosensitisers.

Useful information has been obtained by means of electrode potential measurements of the oxygen tension and oxidation-reduction potential in tumours and some normal tissues. Measurements have shown the influence of inhaled oxygen and of various chemical agents. Evidence has been obtained concerning the optimal time for intravenous administration of Synkavit as a radiosensitiser before X-ray therapy.

The introduction of clinical staging of malignant tumours into veterinary practice is recommended.

Chemotherapy is discussed. Interesting results have been obtained by the use of nitrogen mustard oxide and of tetra-sodium 2:5-dimethylhydroquinone diphosphate (Compound XL).

Much further work is required in these fields.

Acknowledgments.—We would like to thank Professor L. P. Pugh, Colonel J. Hickman and Mr. Rees Evans for referring the dogs to us for treatment, Miss J. L. Young for her help in carrying out the radiotherapy, and Mr. J. L. Haybittle and Miss R. S. Saunders for calibration of the X-ray therapy apparatus and help with the dosimetry and planning of the treatments.

We wish to express our gratitude to Dr. A. L. Morrison and Dr. J. H. Marks, of Roche Products, Welwyn Garden City, for the preparation and the gift of supplies of Synkavit and of Compounds XIV and XL, and to Asta-Werke, Brackwede, for the gift of a supply of Mitomen.

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THE CHAIRMAN

Mr. G. N. Gould, in introducing Professor Mitchell, said: "I am deputising for Professor Bosworth who is absent on account of the serious illness of his wife.

"For many years, veterinary surgeons—particularly those dealing with dogs and cats—have been interested in neoplasms in their patients, and a number of veterinary pathologists from M'Fadyean onwards, have made a more or less close study of tumours. In recent times there has been an intensification of interest in animal tumours, particularly in the U.S.A., since it is realised that a study of these tumours is of importance not only from the point of view of diagnosis and prognosis in the animal itself but also because of the significance of spontaneously occurring cases.

"I was greatly impressed by Professor Banks's comment in his excellent address on Wednesday, when he suggested that the cause of cancer might well be revealed in a veterinary school, and it is very gratifying to see that the regius Professor of Physic in this ancient university is also concerning himself with comparative oncology.

"In the field of radiotherapy, in which Mr. Knight, of the London College, has made such a great contribution, the prime concern will always be the well-being of the animal patient, but nevertheless, close studies of animals so treated must have an important bearing on radiotherapy of human cancers and we shall be intensely interested to hear what Professor Mitchell has to tell us about the results of the work he and Mr. Silver have carried out."

The General Discussion

Mr. A. R. Jennings, in opening the discussion, said that he was particularly interested in Case 5 to which Professor Mitchell had referred in his paper. This was probably the first recorded case of Hodgkin's disease in the dog. There had been a lot of controversy for many years on the question whether true Hodgkin's disease occurred in the dog. Some 8 or 9 years ago he had investigated a series of cases which clinically resembled Hodgkin's disease but which histologically differed from the classical human cases. These cases could best be described as being malignant lymphoma. There was a symmetrical bilateral enlargement of the carcase lymph nodes with lymphoid deposits in many organs. There was a very striking breed incidence, over 80 per cent. of the cases occurred in the Scottish Terrier breed. He had used urethane given *per os* in a number of cases. There had been a very striking clinical response, but it was only a temporary one. As a result of the urethane there was a spectacular fall in the numbers of circulating leucocytes and the dogs appeared brighter. The drop in the leucocytes was, however, only temporary, and the counts gradually increased. The dogs eventually died. He got the impression that urethane was useful for prolonging the life of the dog and to some extent for relieving suffering.

He had treated 2 of these cases with nitrogen mustard hydrochloride given intravenously. This treatment resulted in severe diarrhoea. There was a circulating collapse and the dogs died in the second day of treatment.

Mr. E. Cotchin congratulated Professor Mitchell and Mr. Silver on their excellent paper and on the work which they were doing in this field.

Professor Mitchell had said that the aims of this study were twofold: first, to try to develop practical methods of non-surgical treatment of malignant tumours in dogs, and, second, to gain information in connexion with treating human cancer. The second aim was a most important one, of course, from the human point of view. They should, however, in considering X-ray therapy of tumours in dogs, bear in mind three relevant factors: firstly, did it offer a fair chance of recovery to the dog; secondly, from the owner's point of view, could he afford it; and thirdly, from the veterinary surgeon's point of view, how could he get the diagnosis of malignancy and possible radiosensitivity made and confirmed, and where should he go in order to obtain the necessary treatment? Probably the veterinary schools would remain the chief places where such diagnosis and treatment could be undertaken.

The connexion between tumours in man and animals was fundamentally important. He had been preaching the importance of the study of spontaneous tumours in animals for years, and it was gratifying to have this view confirmed by Professor Mitchell. This study was likely to throw much light on spontaneous tumours in man, and there should be the greatest rivalry between the various veterinary schools to see if they could be the first to fulfil Professor Banks's prophecy that the cause of cancer might well be discovered in a veterinary school.

It had been confirmed by Mr. G. C. Knight in London that the transmissible venereal tumour of the dog was extremely sensitive to X-rays, and this was one of the lesions well worth submitting to X-ray therapy, although it was rarely seen nowadays. Tonsil carcinoma in the dog was also radiosensitive, but this tumour, unfortunately, metastasises quickly, and the metastases are not sensitive. A rare tumour, the "papilliferous epithelioma" of the gum of the dog, is remarkably radiosensitive.

Professor Mitchell had stated that in dogs with malignant tumours there was often not much clinical evidence of widespread metastases, and Mr. Cotchin recalled some illustrative cases of this kind. Regarding the suggested grading of tumours, he thought that there were two important things that had to be known about any given tumour in animals: first, was it of a type that did metastasise, and second, in the individual case, had it metastasized?

On the question of (true) Hodgkin's disease in the dog, Mr. Cotchin said that he agreed with Mr. Jennings. Professor Mitchell's series of cases included one diagnosed as Hodgkin's disease. As it was of great importance to know of such a case having occurred, he hoped it would be reported in the greatest detail.

It had been suggested that histology was a good guide to malignancy in animal tumours. That might be so in some instances, but in the case of mammary tumours, for example, it had been found in a recent series that only 10 per cent. were clinically malignant, whereas 40 per cent. were histologically malignant.

He did not understand the statement in Professor Mitchell's paper that it appeared that mammary tumours in female dogs were becoming more malignant over the past 20 years. Did that mean there were more cases of malignancy, or that the malignancy was greater when it did occur? Some information on this point would be of interest.

Finally, Mr. Cotchin said, he was sure that they would all like to thank Professor Mitchell for the great interest he was taking in veterinary medicine in general, and in veterinary oncology in particular.

Mr. P. J. Dalton said that no one present would have the audacity to cross swords with Professor Mitchell on this subject after such an eloquent dissertation.

When one considered that Hobday and Johnson published articles on radiography in 1896, only one year after the discovery of the X-ray by Roentgen, there was little evidence of the application of radiotherapy to veterinary practice in this country, and it was to be hoped that following Profes-

sor Mitchell's paper a greater interest would be aroused in this subject.

In his practice, said Mr. Dalton, X-ray therapy had long been employed for the treatment of various conditions in dogs and cats, and since August of last year they had employed also beta-rays from a strontium 90 emitter, obtained by the courtesy of the Radio-biochemical Centre at Amersham.

In a small practice such as his, he could not afford the considerable capital outlay required to install a high-voltage machine, and the results that had been obtained had been by means of a machine whose maximum output was 83 Kv. with a maximum H.V.L. of 2m al. To overcome these factors the following methods had been employed: first, fractionation; second, the use of iodine; and third, altering the H.V.L. of the rays during treatments in an attempt to lay down a "creeping barrage" of destructive rays.

It had been found that for the majority of lesions which responded in dogs and cats, fractionation of dosage into four irradiations at 3-day intervals were well tolerated not only by the tissue adjacent to the lesion but also by the animal as a whole. The doses used varied from 150 to 600 Roentgen per treatment. It was possibly significant that in human medicine irradiation appeared to be contra-indicated on Saturdays and Sundays, while in veterinary practice it had been found inevitable that this time-absorbing method of treatment must be carried out at week-ends!

Similar results to those of Dr. Pommer in Germany and the various workers in the United States had been obtained, and it had been found that a large number of conditions in their patients were radio-responsive. These included a wide variety of neoplasms, as well as such conditions as acarthesis migram, cystitis, chronic and mycolic dermatitis, interdigital acne and so-called rodent ulcer in cats.

In the field of beta-ray therapy it had been found that this type of irradiation was the one of choice in lesions of and around the eye, as the extreme sensitivity of the cornea to ionising radiation made the use of the deeper-penetrating X-rays a hazardous procedure. It was a prerequisite of radiotherapy that a close watch be kept on the blood picture of the patient, and he and his colleagues had attempted to follow the white-cell picture. During the examination of the E.S.R. in an attempt to detect any occult metastes when cases of neoplasia were presented for X-ray therapy, it was noticed that there was a considerable difference in the E.S.R., and more especially in the final level of pre- and post-irradiation samples. This seemed to be closely linked with the radiosensitivity of the lesion irradiated, and he and his colleagues believed that they could now determine whether or not any particular neoplastic lesion would respond to irradiation by an examination of the E.S.R. of blood taken before and after the first treatment. This finding was not only of importance in the practical application of radiotherapy but might also be of some import in wider fields. He hoped that others, better equipped, would look into the problem.

The speaker concluded by expressing regret that he had been unable to attend the opening of the Congress. He believed that the profession had been called to task for neglecting "our feathered friends," and he wished to record that he and his colleagues had treated successfully, by beta-ray therapy, a case of neoplasia of the face of a budgerigar.

The Chairman: "I am sure that Professor Mitchell's address and the short discussion which has been permitted has impressed us all with the vast importance of the comparative study which he is directing and in which he is taking such a close personal interest. I am sure we look forward to further communications on this subject which will have a very important bearing on the problem of cancer in all species. Professor Mitchell, we thank you.

The Reply

Professor Mitchell, in replying to the discussion, said that he was grateful to Mr. Cotchin for his criticism of the proposed method of staging tumours in animals. That was the sort of thing which he had hoped would be said. In human medicine it was difficult to know whether tumour had metastasised. The discrepancy between histology and the biological malignancy was a great problem in human medicine.

He agreed with Mr. Dalton about the value of radiotherapy in non-malignant conditions, including ophthalmic conditions. He pointed out, however, that one had to observe caution because of possible side-effects in man, which did not arise with animals. He suggested that his work on the sedimentation rate should be published.

The Diagnosis and Surgical Treatment of Some Abnormal Stifle Conditions in the Dog

BY

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Introduction

SEVERAL factors contribute to make the stifle joint unique and complex in structure, intriguing in function, but relatively susceptible to injury.

Not only do injuries to structures outside the joint occur but the presence within the joint of menisci and crucial ligaments make severe intra-articular injuries a common feature of stifle lameness. Initial injuries are invariably associated with ligaments and as the effect of the stresses causing the injuries frequently affect more than one structure, exact diagnosis of stifle lameness is not an easy matter and requires experience and skill in digital palpation together with a sound radiological technique.

Surface and General Anatomy

Before accurate diagnosis can be achieved a knowledge of the structural and functional anatomy of the stifle is essential. This has been dealt with effectively by Dyce *et al.* (1945), but it may not be amiss to mention certain anatomical details which have a direct bearing on diagnosis and surgical treatment.

On the anterior aspect of the limb the tibial crest forms the most prominent bony landmark located vertically beneath the articulation. Moving upwards, this bony ridge gives place to the tough fibrous middle or straight patella ligament. If this ligament is followed proximally it becomes less defined as it runs in the groove of the trochlear before merging with the patella. Above this saddle-shaped bone the quadriceps group of muscles form the muscle mass anterior to the femur.

Below the joint the medial aspect of the tibial crest can be palpated merging with the medial tibial condyle. It must be appreciated that the condyles of the femur articulate with the tibial condyles on the posterior plane of the joint. Consequently a relatively large space, triangular in outline when viewed medially or laterally, exists in the anterior aspect of the joint. This triangle is bounded anteriorly by the straight patella ligament, proximally by the femoral condyles, and distally by the tibial condyles. The area is soft to the touch, and palpation reveals the infrapatella pad of fat which lies behind the middle patella ligament. It is not possible to palpate the medial and lateral patella ligaments as both are weak and relatively insignificant structures, particularly the lateral, which in puppies and young dogs is almost non-existent.

Deep palpation from the medial aspect directed to the area posterior to the stifle joint reveals the insertion of the medial head of the gastrocnemius and the medial sesamoid bone or fabella.

Proximal to the stifle joint on the medial aspect it is possible to define anteriorly the posterior border of the sartorius muscle and posteriorly the gracilis muscle with its border running over the medial aspect of the stifle.

On the lateral aspect of the joint the main landmark is the lateral tibial condyle attached to which is the head of the fibula. The lateral head of the gastrocnemius can be identified but it is difficult to locate individual muscles above the joint owing to the large area covered by the tensor fascia lata.

The femorotibial articulation is strengthened firstly by the strong medial and lateral collateral ligaments, secondly by the muscles which arise within the joint capsule—the popliteus and the extensor digitorum longus. The former arises from the lateral condyle of the femur and passes posteriorly *via* the popliteal notch of the tibia diverging to an extensive insertion on the medio posterior aspect of the tibia. The extensor digitorum longus arises from a rough depression between the lateral condyle and lateral lip of the trochlear, passes across the lateral aspect of the joint through a shallow notch in the lateral meniscus and an equally shallow notch between the lateral tibial condyle and the tibial tuberosity before becoming a fleshy muscle, which later divides into four parts at the tarsus. For approximately ½ to 1 inch, as it passes over the groove in the proximal part of the tibia the tendon of this muscle is enclosed by a synovial sheath which is a diverticulum from the main joint capsule.

Within the joint are the two cruciate ligaments, connecting the femur with the tibia. The anterior, which is most frequently damaged, passes obliquely from the head of the tibia just in front of the tibial spine and between the cornua of the menisci to the medial aspect of the lateral femoral condyle. The posterior and longer ligament of the two runs from the medial surface of the popliteal notch of the tibia to the lateral surface of the medial femoral condyle. The ligaments twist upon each other.

The two fibrocartilaginous menisci make good the incongruity between the tibia and the femur. They have thick outer edges attached to the capsule, from which their peripheral blood supply is derived, and they taper inwardly. As the name suggests both menisci are crescent shaped, the lateral being slightly larger than the medial, and are attached to the head of the tibia by four ligaments, two anterior and two posterior. In addition an intermeniscal ligament attaches the menisci anteriorly whilst posteriorly there

is a lateral femoromeniscal ligament. These ligaments govern the movement of the menisci over the surface of the tibia.

Fibrocartilaginous structures are normally found as expansions on either side of the patella. Also fibrocartilage plaques are found in the tendons of the quadriceps in close apposition and overlapping the lips of the trochlear. The plaque in the tendon of the medial vastus muscle is developed to the greater extent and perhaps helps to prevent lateral displacement of the patella. In connexion with cartilaginous structures it must be remembered that the lips of the trochlear are thus constructed and that patella luxation frequently damages the lip.

Finally the joint capsule extends above the upper limits of the trochlear over the anterior surface of the femur thus facilitating the movement of the muscle group at this point.

Functional Anatomy

It is readily apparent that over-flexion of the stifle joint is difficult because of the thigh muscles, whereas the bony structures cannot prevent over-extension, consequently all the strain of over-extension is borne by the ligamentous structures. Normally the anterior and posterior cruciate ligaments appear to be under approximately the same tension, but the anterior being shorter and slightly stouter bears the major part of the strain of over-extension, the posterior cruciate acting to some extent as a check ligament in view of its greater stretching potentialities.

The menisci move forwards in extension and backwards in flexion thus appearing to be at all times in the best position to act as buffers at the points of greatest pressure.

Lateral and medial movement of the tibia on the femur is governed mainly by the medial and lateral collateral ligaments respectively, by the cruciate ligaments and the capsule, and also by the deep fascia and aponeurosis of the thigh muscles laterally and the gracilis tendon of insertion medially.

It is also readily apparent that the tibial tuberosity takes the full tension of the extensor muscles in contraction and that the patella is merely a sesamoid bone, the purpose of which is to ensure a smooth, gliding movement of the common ligament of the quadriceps in the form of the middle patella ligament over the femoral trochlear. By ensuring this action the full leverage of the two long bones is maintained by the action of the quadriceps.

The extensor power of the quadriceps muscles is dependent entirely upon the gliding motion of the patella over the trochlear. If, as occurs in medial luxation, the patella slips off the trochlear there is a tendency towards flexion of the joint rather than extension, owing to loss of the pivoting action of the patella on the trochlear.

The function of the synovial fluid is well known, but some consider that a useful effect of the presence within the joint of menisci is to increase the surface area over which the fluid can exert its lubricating action and dissipation of heat.

Clinical Examination of the Stifle Joint

A considerable amount of information can be obtained by watching the dog at rest in the standing position. It should first of all be viewed from behind and note taken as to whether the hock is abducted or adducted and consequently the stifle taking converse positions, bearing in mind that the stifle is normally slightly abducted and the hock similarly adducted in relation to an imaginary straight line drawn from the hip joint to the toes. From the side, it should be noted whether the stifle is greatly flexed with the foot raised from the ground or whether the toes are just touching the ground; also whether the limb is being held forward or backward.

Movement is best observed with the dog loose in a run moving freely, it can then be seen if the limb is being extended, forward or backwards, if held high or with the toe just touching the ground but not bearing weight, or whether an attempt at weight bearing is being made. It should also be seen whether or not the limb is being used almost normally for a few paces and then lifted suddenly and carried.

Having made these observations the dog should be placed on a table for palpation and manipulation of the limb. On no account should this examination precede that just described, as manipulation of an injured limb during examination can affect movement for some time afterwards, also it is advisable to follow the second part of the examination with anaesthesia and radiological examination.

Having eliminated superficial injuries as a cause of the lameness, the foot and hock should be examined closely and as far as possible eliminated as sites of injury. By holding the stifle firmly in the palm of the hand and fixing it, the femur should be moved backwards and forwards, abducted and adducted and rotated, to eliminate as far as possible the presence of an injury to the hip. Auscultation over the hip using a stethoscope is a useful adjunct to this stage of the examination. It must be pointed out that this method of examination is only undertaken if a stifle injury is suspected from the action previously observed, also that it is a personal preference of the writer to eliminate as far as possible other common sites of injury, such as the foot, hock, and hip, before getting down to thorough examination of the stifle.

A landmark is quickly obtained by holding the limb just above the hock in one hand with the stifle slightly flexed and with the first finger and thumb of the other hand run up the front of the limb from the proximal third of the tibia, until the lower part of the tibial crest is defined. The fingers should continue upwards until the proximal extremity of the tibial crest and insertion of the middle patella ligament is felt. The tension of the ligament can be ascertained and continuing upwards the lips of the trochlear become apparent. The patella should be easily located even in the smallest dog, and its position relative to the trochlear determined. By again bridging the patella ligament with finger and thumb the soft area medially and laterally can be palpated; normally it is slightly depressed and it is possible to feel the pad of fat lying just behind the ligament.

Any distension of the joint can be felt at this point, also increased heat and pain. Moving finger and thumb backwards and slightly downwards, the medial and lateral limits of the femorotibial articulation can be determined and particularly in old dogs with chronic lesions of the joint any increase in width can be ascertained. Frequent comparisons with the opposite joint, if normal, will prove helpful in deciding upon the existence of an abnormality.

It is next necessary to determine the freedom or otherwise of movement of the two articulations of the joint, also to note any sign of pain which is usually made apparent by the dog turning his head to the side being examined. Useful information can be gained by the use of the stethoscope over the joint. An assistant should hold the head of the instrument in place, *i.e.* over the lateral and then the medial aspect of the femorotibial articulation, and the examiner, holding the femur firmly, extends and flexes the limb. Normally only a slight click is heard at full extension.

To complete the examination anaesthetise the dog using a short acting barbiturate such as thiopentone sodium. The above examination should be quickly repeated but in addition it is necessary to estimate the degree of mobility of the patella, also the degree of mediolateral movement of the tibia on the femur. Both these examinations are best applied with the limb in extension. The femur should be gripped firmly in one hand and the tibia gripped firmly in the other at a point just below the tibial condyles. In a normal joint the degree of mediolateral movement of the femorotibial articulation is very small indeed. Next, by placing the thumb of one hand over the area between the two sesamoid bones and the fingers grasping the lower thigh, the tibia is taken in the other hand and the anterior posterior mobility ascertained. This examination is particularly important in determining the condition of the cruciate ligaments and in the normal joint this movement is also negligible.

Radiological Examination

The anterior posterior view is taken with the dog lying on its chest, the limb extended backwards, giving approximately 120° angle at the stifle joint. In order to overcome the slight degree of normal abduction to the stifle raise the opposite hind quarters an inch or two so that the stifle to be examined acquires absolute alignment with tube and cassette or film. In this position the patella lies close to the film and is clearly defined. A fine-grain film such as Ilfords Ilfex gives excellent quality for these radiographs.

The radiological technique described by Hickman (1954) using a curved cassette for examination of this joint will no doubt have many advantages, but has not been used by the writer.

The lateral view is taken with the affected side lying on the cassette or film. It may be necessary to raise the hip of the same side ½ to 1 inch to allow the stifle to lie flat on the film and assure good alignment. For both positions it is essential to see that the tube is directly over the stifle joint so that extraneous shadows are reduced to the minimum. Again it is helpful to X-ray the opposite leg for comparison, and it may occasionally be necessary to take oblique views although these can be confusing to read. The injection of 15 to 30 c.c. of air as a contrast medium (Dyce *et al.*, 1954; Hickman, 1954) is a most useful addition to the radiological technique and points relating to its practical application will be mentioned later.

The examination of the stifle has been dealt with in some detail as it is considered essential to make a thorough and complete examination and to establish a routine procedure. Without such an approach stifle injuries are difficult to define with accuracy.

The Diagnosis of Stifle Abnormalities

Luxation of the Patella

This is perhaps the easiest stifle condition to diagnose. The luxation is most frequently medial and can be congenital in origin or as a direct result of trauma. In some cases recurrent luxation occurs causing the limb to be intermittently carried; in others luxation is complete and even if manipulated back into position, immediately reluxates. When carried, the limb is noticeably flexed, the stifle is adducted, the hock abducted, and the foot pointing diagonally inwards, the toes sometimes passing across the medial line. In some cases of recurrent luxation of some duration the dog is able to replace the patella by stretching the limb backwards in extension and rotating the tibia laterally. The patella will frequently remain in place whilst the dog is running, but luxation recurs at the walk. In other cases the limb is used normally at the walk for several paces, then carried according to whether the patella is in position or not.

When a bilateral luxation exists both stifles and tarsus are flexed and the dog moves in a crouched position, whilst some will move remarkable distances on the fore limbs with the hind limbs elevated.

On palpating a case of luxation commencing at the tibial crest the middle patella ligament is found to run medially and when followed upwards the medial lip of the trochlear is felt and the trochlear itself can be defined through its whole anterodorsal aspect. The patella is found lying medially, but if the limb is extended it can usually be replaced with ease. In the rarer cases of lateral luxation, corresponding changes are found.

When examining cases of recurrent luxation, the patella may be found in its normal position, but on flexing and extending the fore limb, the bone may be moved on and off the trochlear with ease.

Anaesthesia and radiological examination is seldom necessary to confirm diagnosis but screening can be helpful, particularly in very small dogs such as the Griffon in which this condition is common. In such animals the patella, is often in its normal position with the limb extended, but on flexion the patella is seen to move within the trochlear for a short distance before luxating.

In severe cases the upper part of the medial lip of the trochlear may be completely broken down and the articulating cartilage of the patella on its lateral side severely eroded, a grating can be heard and felt

as the patella is made to move on and off the trochlear. The prognosis on such cases is not good.

Treatment. Congenital cases. In small breeds surgical interference is the only line of treatment worth considering. In medium and large breeds, rest in a plaster cast for three to six weeks is justified, but the vast majority require surgical interference. In adult dogs of all sizes in which luxation has occurred through injury, counter-irritants or rest in a plaster cast frequently give results and should be applied before resorting to surgery.

Sprain of the Medial and Lateral Collateral Ligaments

Sprain of the medial ligament is the commonest, and results from excessive outward angulation of the tibia on the femur.

The injury is acute and painful but the limb is not always carried although the limp may be severe. The limb is not fully extended forwards and the dog tends to walk slowly taking short steps. On palpation a diffuse swelling can be located over the femorotibial articulation which is divided in the case of the medial sprain by the gracilis and sartorius tendon. The swelling is seldom great and careful palpation and comparison with the opposite limb is required to reach a diagnosis. Owing to the tougher fascial covering on the lateral aspect the swelling on this side is sometimes imperceptible. If the dog is anaesthetised, a greater amount of angulation is possible on the affected side but auscultation does not reveal abnormal sounds on flexion and extension of the joint, and the antero-posterior movement of the tibia on the femur, which is associated with injury to the cruciate ligaments, is not apparent.

Treatment. Complete rest which can only be assured by immobilising the limb.

Sprain of the Common Tendon of Insertion of the Sartorius and Gracilis Muscles

This is encountered most frequently in older dogs, especially the working gun dog. It is a painful condition causing acute lameness and cannot be distinguished from the foregoing conditions except by digital palpation. The common tendon is formed from the posterior band of the sartorius and the gracilis muscle; sprain of this tendon and the medial ligament commonly occur together, but the tendon injury heals more slowly, consequently its presence is sometimes not apparent until the general diffuse swelling of the ligament injury has subsided. When this occurs the tendon can be felt as a broad band as it passes over the medial aspect of the stifle. Flexion of the joint is particularly painful in this condition. Using a fine-grain film and exposing for the soft tissues it is possible to demonstrate inflammatory changes, using the A/P position.

Treatment. Enforced rest is again the treatment of choice and a plaster cast applied when the localised swelling has subsided gives satisfactory results. In a recent case treated by the writer, occurring in a 10-year-old working springer spaniel, the stifle injury involved the medial ligament, the gracilis tendon, and also rupture of the lateral patella ligament which caused a medial luxation of the patella. The latter condition was corrected by reinforcing the lateral patella ligament by the Otto Stader technique and the post-operative immobilisation in plaster produced complete recovery of the medial injuries.

Meniscal Injuries

The medial meniscus is the most vulnerable to injury. Nilsson (1949) reports that out of 60 dogs operated on at the Royal Veterinary College, Stockholm, 50 involved the medial meniscus alone.

The anatomical structure and histopathology of the menisci has been admirably described (Paatsama, 1954). The author studied 20 cases of meniscal injury and found that the medial meniscus showed changes in 15, whilst only in three were the changes limited to the lateral meniscus.

However, the important points are, firstly, that the collogen fibres of the fibrocartilage are arranged in undulating bundles running parallel to the peripheral border; secondly, that rupture of a meniscus invariably follows the line of these collogen fibres; thirdly, that regeneration of a meniscus takes place only from the joint capsule in the form of a granulating membrane, which appears to be equal in functionable ability to fibrocartilage. Lastly, that healing of a meniscal rupture can only take place if the injured part is in contact with the joint capsule. As this seldom happens and the damage invariably occurs in the avascular part of the fibrocartilage, spontaneous healing very rarely takes place (Nilsson, 1949).

This injury is not easy to recognise and frequently cases are brought to the veterinary surgeon's notice only when chronic lameness is established. There is usually no history of trauma but the onset of the lameness is sudden. The leg is invariably carried at first, although the chronic case limps and when running may even use the limb although movement of the stifle joint is minimal. When carried, the stifle is slightly flexed and the toe is carried forward.

In the acute case there is usually a tenseness and swelling on either side of the middle patella ligament.

Pain is particularly apparent on flexion of the joint and distinct crepitation may be heard on auscultation. In many cases, particularly some days after the initial injury, the crepitation can be heard without aid.

The case should always be anaesthetised in order to try to decide whether or not rupture of the anterior cruciate ligament has also occurred as the two conditions frequently co-exist. Forward and backward manipulation and rotation will help considerably in making a decision. When taking a radiograph it is essential to observe correct positioning as previously described so that the rays pass exactly parallel to the articulating plane. The other limb should always be taken for comparison. In cases of meniscal rupture there is a narrowing of the fissure between the articulating surfaces. It is important, however, to appreciate that the fissure found on the medial side is normally less than that on the lateral in keeping with the slight degree of normal abduction of the stifle.

In chronic cases early arthritic changes can be demonstrated radiographically with a thickening of

FIG. 1.—Lateral view of normal stifle.

FIG. 2.—A/P view of normal stifle.

FIG. 3.—Lateral view of case with rupture of the anterior cruciate ligament. Note the " riding forward " of the tibia.

FIG. 4.—A/P view of case with rupture of the medial meniscus. Note the narrowing of the fissure between the medial condyles.

FIG. 5.—Lateral view of an early case of osteoarthritis of the stifle joint. Note the " spur " formation on the distal extremity of the patella, the posterior aspect of the joint surface of the tibia *and* the upper extremity of the lip of the trochlear.

FIG. 6.—A/P view of a more advanced case of osteoarthritis with changes apparent on the femoral condyles (medial and lateral aspects) and the medial aspect of the tibial condyle. Also increased density of the menisci.

FIG. 7.—Lateral view of case with osteoarthritis of the stifle joint with " joint mouse " clearly shown.

FIG. 8.—Lateral view showing avulsion of the tibial crest in a 7½-month-old Pug.

FIG. 9.—Showing operative position for tibial transplantation.

FIG. 10.—Showing operative position for repair of the anterior cruciate ligament.

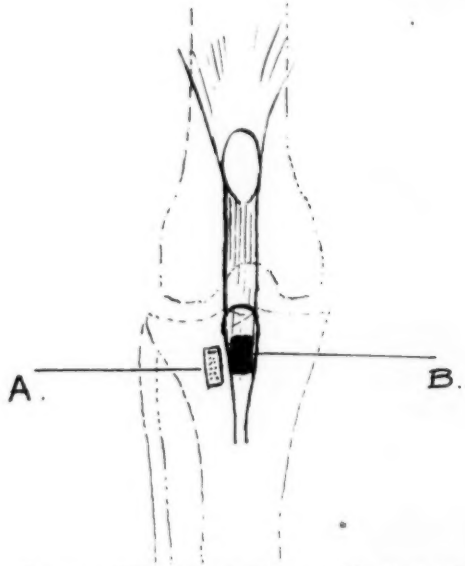

FIG. 11.—Tibial transplantation. The block of bone " B " is grafted to the new site at " A."

the joint capsule on the affected side and opacity of the meniscus itself.

Reading of X-ray films must be undertaken cautiously although the use of air as a contrast medium helps considerably in defining the menisci and cruciate ligaments. It is perhaps wise to depend more upon digital palpation and manipulation, using X-ray to confirm diagnosis rather than to establish it.

In cases of chronic lameness where meniscal damage is strongly suspected but where doubt nevertheless remains, arthrotomy is fully justified. By this procedure a diagnosis can be definitely established and in positive cases of meniscal damage whole or partial extirpation can be undertaken. In negative cases no harm is done by such an operation provided aseptic technique is applied.

Treatment. Rest is of little avail as a torn meniscus seldom heals spontaneously. Results with the intra-articular injection of hydrocortisone preparations have yet to be assessed but although this treatment will no doubt give relief by reducing the inflammatory changes involved, it is difficult to imagine that anything further can occur.

Surgical intervention is indicated if lameness has not disappeared after a period of three weeks.

Rupture of the Anterior Cruciate Ligament

Diagnosis of this condition is made easier by appreciating that one of the functions of the anterior cruciate ligament is to prevent the tibia from moving forward on the femur. It is known that rupture of the anterior ligament invariably occurs before rupture of the posterior.

Various theories as to the cause of this condition have been propounded (Dyce *et al.*, 1954; Paatsama, 1952; Schnelle, 1950; and others), but it is generally agreed that hyperextension, hyperflexion, and possibly rotation are considered to be commoner causes than direct trauma.

The lameness associated with this lesion is acute, and from watching the dog at rest and in movement it is not possible to appreciate any striking difference in posture from that associated with meniscal injuries. The toes seldom touch the ground in the early stages and as with all severe stifle injuries disuse atrophy, particularly in the quadriceps, is quickly apparent. On manipulation pain is less marked than with meniscal injuries but it is common to find that as the limb is straightened a clicking is most noticeable as the tibia suddenly slides forward on the femoral condyle. The result is that the tibial crest is thrust forward in relationship to the femur and the relatively flat region anterior to the articulating surface of the tibia is palpable.

This clicking forward of the tibia is not readily apparent in all cases and it is always wise to anaesthetise and manipulate the limb. A distinct forward movement is obtained by anteroposterior manipulation with the joint in its normal " standing " position, but on flexion the " draw forward " action can usually be demonstrated.

Without these clinical features radiological examination can again be deceptive, although the use of air as a contrast medium and careful positioning and exposure using a fine-grain film helps tremendously. Descriptions of this condition suggest that the forward position of the tibia is readily apparent and that the femur appears to articulate on the posterior aspect of the tibia. This is of course the normal state of affairs but breed variation, particularly with regard to the tibial crest, is tremendous and interpretation is difficult particularly in the smaller breeds such as the Corgi and Scottie, which have very prominent tibial tuberosities giving the impression that the femur is articulating abnormally far backwards.

As the anterior cruciate ligament invariably tears from its distal attachment it is sometimes possible in cases of long standing to detect an opaque fragment " joint mouse " lying in the joint cavity. When rupture of the anterior cruciate ligament has occurred, rupture of the menisci, particularly the medial, may be co-existent. The determination of the latter condition when associated with the former is difficult and arthrotomy is justified in order to clarify the diagnosis.

Treatment.—As the ruptured ligament seldom, if ever, regenerates (Paatsama, 1952, and Pfab, 1933) there is little point in resting by immobilisation. As the inflammatory changes associated with the injury abate, the dog will use the limb again although lameness remains. Possibly, in view of the decreased pressure on the fibrocartilaginous menisci, degenerative changes occur in these structures. Experimentally these changes occur in 50 days following the severing of the anterior cruciate ligament (Paatsama, 1952). Consequently surgical repair of the anterior cruciate ligament can be undertaken and will later be described.

Osteoarthritis of the Stifle Joint

In common with most osteoarthritic changes this condition is most frequently seen in the older dog, although it is not uncommon to find early changes at four to five years of age.

Onset is slow and commences as an imperceptible limp becoming gradually more severe as time passes. If seen early the owner can sometimes remember a sudden injury occurring a varying time beforehand.

On palpation the mediolateral diameter of the femorotibial articulation is generally greater than the other limb, but palpation, flexion, and extension do not produce marked pain. It is necessary to eliminate so far as possible meniscal injury both by clinical and radiological examinations.

Diagnosis is not difficult from radiographs taken in the A/P and lateral positions and it is possible to detect quite early changes. These are most frequently found associated with the lips of the trochlear, the distal end of the patella and the posterior edge of the articulating surface of the tibia. Radiologically the early changes on the trochlear and tibia are in the form of diffuse " deposits " which obscure the clear-cut line of the joint surface. The distal end of the patella shows " spur " formation and in later cases " lipping " occurs around the edge of the tibial articulating surface usually particularly marked

posteriorly. Increased density of the menisci may also be seen in the later stages of the condition.

Prognosis is bad in these cases although rest and intra-articular injections of hydrocortisone preparations occasionally give temporary relief.

Avulsion of the Tibial Tuberosity

This condition occurs in puppies before the age of 10 months, usually in the larger breeds, although cases do occur in the smaller breeds if the individual is grossly over-weight and fusion of the tibial tubercle with the diaphysis is delayed. There appears to be considerable breed and individual variation in the time taken for this fusion to occur. Until more work has been carried out on the normal development of the tibia with particular reference to the fusion just referred to, it is difficult to differentiate between the congenital condition which resembles Osgood-Schlatter disease in man and avulsion due to trauma.

Whatever the cause the symptoms are similar. The dog prefers to remain recumbent and has difficulty in rising. The limb or limbs, if bilateral, are held back so that the femur is almost vertical. The thighs are abducted and the hocks and feet held close together. Movement is difficult and the hind limb is not extended forward, consequently, especially in the bilateral cases, the movement becomes swaying and awkward and there is a lack of co-ordination between the movement of the fore limbs and the hind limbs. Palpation of the stifle shows a certain amount of pain and diffuse swelling of the joint. If the tibial tuberosity is gripped firmly between finger and thumb a certain mobility can be detected.

A radiograph in the lateral position shows an abnormally large gap between the tubercle and the diaphysis There is a rarefaction of the tibial tubercle and the distal extremity is pulled away, leaving a frayed appearance to the tibial shaft.

Before confirming the diagnosis it is necessary to eliminate rickets as a cause of the abnormal stance and movement by clinical examination and by examining other long bones, particularly the radius and ulna for evidence of "epiphyseal mushrooming."

Treatment. Immobilisation in extension preferably by use of a plaster cast for three to four weeks together with vitamin therapy.

Supracondyloid Fractures of the Femur

These frequently involve the joint and may occur wholly or partially at the epiphysis. In any case the diverticulum of the joint capsule extending some distance above the limits of the trochlear is usually involved.

There is often a history of an accident and pain is considerable. In young animals it is possible to feel crepitation on manipulation, but in adult dogs, owing to the contraction of the quadriceps, the fracture is effectively immobilised, but riding upwards of the main shaft is often relatively great. No difficulty exists in diagnosis following radiography and the use of the transfixation screw is highly satisfactory in the majority of cases. The operative technique for the insertion of this screw has been described by Knight (1956).

The Surgical Correction of Patella Luxation

This operation involves the total or partial transplantation and grafting of the tibial crest into a position slightly lateral to the normal position so as to exert lateral tension on the middle patella ligament (*i.e.* in cases of medial luxation).

Following anaesthesia, with the dog lying on its back, the three sound limbs are secured in extension and the limbs on the side to be operated upon are secured with a sandbag below the stifle (as shown in Fig. 9). The area having been clipped and shaved is draped with sterile cloths taking care that they are securely fastened to cover the underside of the limb. Application of sterile tubergauze is most useful and ensures complete coverage.

A longitudinal incision is made from a point 1 inch above the patella extending to approximately ½ inch below the tibial crest in the midline.

The skin reflects easily to either side; haemorrhage is slight. The delicate subcutaneous tissue is reflected layer by layer until the middle patella ligament and the tibial crest are exposed.

The anterior tibial muscle is then separated from the anterolateral aspect of the tibial crest from the distal end of the crest, proximally to almost, but not including, the subsidiary origin of this muscle at the lateral tibial condyle. Reflection of this muscle is not difficult and the entire lateral surface of the tibia in this region is readily exposed. At this stage the surgeon may make a choice of two procedures: both involve the transplantation and the grafting into a lateral position of whole or part of the tibial crest. In the small breeds the author prefers to carry out the operation based on the Hauser technique in the human, but in the larger breeds, this has the disadvantage that whilst in the human the tibial crest is a mere mound, in the dog the crest is a distinct ridge and is an important factor in leverage, consequently the crest as a whole should be transplanted in the large breeds and the short-legged breeds with prominent crests, thus retaining its proper function.

The Hauser technique involves the removal of a rectangular portion of bone from the lateral aspect of the tibia as indicated in Fig. 11, using ⅛ or ¼ inch osteotome. This is taken through the cortex of the bone and must be carried out with extreme care; in a griffon or miniature poodle the piece removed should measure approximately 5 by 3 mm. At a point where the insertion of the middle patella ligament on the tibial crest ends, a 4 mm. incision is made vertically into the crest using a bone saw. A scalpel is then placed sideways with the blade edge facing distally and inserted between the bone at the proximal end of the crest and the middle patella ligament and an incision made for a few millimetres so that the tendon is separated from the bone for this distance. A fine saw blade is then threaded between bone and tendon and another vertical incision made to correspond to the first about 5 mm. proximal to it. The piece of bone to be excised with the middle patella ligament attached must fit exactly into the space previously provided for it. The block of bone is finally separated from the crest by the use of the

osteotome and left free until the next procedure is complete.

In the small dog it is difficult to retain the graft in position except by stainless steel wire sutures threaded through fine drill holes in the block of bone constituting the graft and in the medial side of the tibia adjacent to the "window."

Having placed the block of bone into its new position, the wire it tightened and secured by twisting. An end of wire approximately ¼ inch long is left pressed close to the bone. After replacing the anterior tibial muscle the subcutaneous tissue is brought into apposition using linen thread; interrupted nylon sutures are used to close the skin incision. The wound is covered by a piece of urosulphonet dressing and the limb from below the hock, but not including the toes, is placed into a plaster cast. The limb is used almost immediately but after the plaster has been removed the dog limps slightly; this should not persist for more than three to six weeks. Owing to the new position of the middle patella ligament there is usually a degree of adduction of the stifle, but as the joint accustoms itself to the new conditions the limb straightens and is used normally.

The alternative method is to remove the tibial crest almost entirely. The periosteum and superficial layer of bone cortex is curetted away on the lateral aspect of the tibial crest to make a seating for the graft. The crest is drilled before removal by sawing and retained in its new position by making corresponding drill holes through what remains of the crest from the lateral aspect to the medial aspect and securing the graft by stainless steel wire sutures or screws.

No originality for these operations is being claimed as both are based on the Hauser technique and the writer had the privilege of first seeing the technique of transplantation of the crest carried out by Mr. Gordon C. Knight, F.R.C.V.S., some years ago. Since then very pleasing results have followed the application of both these operations.

In older animals which have sustained patella luxation as a result of accident and in which the lateral patella ligament has been seriously torn the operation of reinforcement of the external ligament by the use of a fascial strip from the tensor fascia lata according to the technique of Otto Stader (1949) is frequently satisfactory. The only point to emphasise is that the fascial strip should be secured firmly to the medial aspect of the lateral sesamoid or fabella and added security given by a nylon suture on the lateral aspect of the sesamoid.

The writer has seldom found this technique satisfactory in cases of congenital origin.

Meniscectomy

This operation may be partial or complete and as the medial meniscus is most frequently injured the operation for medial meniscectomy will be only briefly described as the subject has been adequately dealt with by Nilsson (1949).

With the injured leg lying on the table the medial area of the stifle joint is shaved and prepared. A skin incision is made from a point just medial to the patella, curving diagonally backwards to a point a little below the medial tibial epiphysis. The broad common tendon of the gracilis and sartorius is retracted. Having deflected any underlying adipose tissue the joint capsule is cut in line with the meniscal edge; haemorrhage is frequently severe at this stage and is best controlled by compression. The synovial membrane is then incised and synovial fluid escapes. This opening is increased anteriorly and posteriorly with scissors. By having the joint adducted, a good view of menisci and cruciate ligaments is obtained. Depending upon the position and extent of the meniscal injury, whole or partial meniscectomy is performed. The anterior and intermediate or posterior meniscal ligaments are severed and the periphery of the meniscus is carefully dissected from the joint capsule for the required distance, remembering that the new granulation tissue which will replace the fibrocartilage removed can only grow from the joint capsule. Loose fibres are removed if only partial meniscectomy is being carried out. Haemorrhage is always profuse and can only be checked by compression. The joint capsule is closed by Lambert sutures of linen, care being taken not to puncture the synovial membrane. The retracted ligament is replaced and subcutaneous tissue and skin are sutured in the orthodox manner. The limb should then be placed in a Thomas splint or plaster for approximately 10 days. It is essential to ensure that exercise is limited after the limb is freed and normal function should not be expected for 6 to 10 weeks.

Repair of the Anterior Cruciate Ligament

Following general anaesthesia the limb is placed as shown in Fig. 10, with the stifle adducted and supported beneath by a sandbag. A greater area is shaved than in the case of tibial transplantation extending from the hip to 2 inches below the stifle over the anterolateral aspect of the limb.

It is advisable to make an exploratory examination of the joint by making a longitudinal incision through the skin from a point 1 inch above the patella to the distal limit of the tibial crest parallel to and about ⅓ inch lateral to the middle patella ligament.

The skin and subcutaneous tissue are reflected with care, the lateral patella ligament is incised from a point opposite the proximal extremity of the patella to ½ inch below the origin of the tibial crest. On reflection of the joint capsule and lateral patella ligament the interior of the joint can be examined, particularly if the joint is flexed. Having verified the presence of a ruptured ligament and the state of the menisci, the operation can proceed. The skin incision is extended upwards to a point in the region of the greater trochanter.

Subcutaneous tissue is cleared until the tensor fascia lata is clearly seen. This fascia is relatively detached over the lateral vastus muscle and it is from this area that a strip of fascia is cut, 1 cm. wide and as long as possible. This is best performed with scissors and it is left attached distally at a point opposite the lateral condyle of the femur. This fascial strip is rolled in gauze soaked in saline until required. The separated edges of the tensor fascia lata can then be sutured with linen thread.

The incision in the lateral patella ligament is extended proximally and the patella is gently pushed from the trochlear to the medial side of the medial lip of the trochlear thus improving access to the joint.

Using a ⅛-inch drill, a hole is made through the lateral femoral condyle so that it emerges into the inter-condyloid space. This is approached by blunt dissection between the flesh head of the gastrocnemius muscle and the semimembranosus muscle, taking care not to damage the posterior femoral artery, saphenous parva vein, and branches of the tibial nerve which are located in this region.

Another hole is drilled from the medial side of the lower end of the tibial crest directed dorsally to emerge at approximately the normal point of attachment of the anterior cruciate ligament but not encroaching upon the articulating surface of the tibia. The fascial strip is then threaded through the first tunnel made in the condyle, passed across the joint and through the second tunnel in the tibial crest. The strip is pulled tightly, flattened out and secured by screws, one of which passes through the tunnel, the other through the ligament as it emerges from the distal end of the tibial tunnel.

Threading the fascial strip is most easily carried out by passing a length of stout nylon through the tunnels the reverse way using small Swiss-pattern aural forceps or similar instrument, firmly securing the fascial strip to the nylon and then gently drawing back until the desired position and tension have been obtained.

After securing the fascial strip the patella is gently returned to its position in the trochlear and the lateral ligament sutured using Lambert sutures of linen thread or fine nylon, the synovial membrane should not be punctured. Subcutaneous tissue is drawn together and sutured; interrupted nylon sutures are used to close the skin incision.

The limb is placed in plaster for two weeks and usually good use is being made of the leg three weeks after its removal. The dog should be sound after 8 to 10 weeks. This operation has proved entirely satisfactory in the small number of cases so far treated, but time is required before a true evaluation of the technique can be made.

In all the operations described, the administration of a long-acting penicillin preparation is advisable, preferably given 12 hours prior to surgery, and aseptic technique must be stringently observed.

Summary

The general and functional anatomy of the stifle joint in the dog is briefly described and the procedure for examination is set out. Methods for the diagnosis of some stifle abnormalities are outlined, and techniques for the surgical correction of patella luxation, meniscectomy, and repair of a ruptured anterior cruciate ligament are described.

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It is hoped to demonstrate the technique of tibial crest transplantation and repair of the anterior cruciate ligament by 16 mm. colour film when this paper is presented.

THE SPEAKER'S INTRODUCTION

Mr. Singleton said that, before showing a film, he wished merely to stress one or two principles in the diagnosis of stifle abnormalities in the dog. In the first place, one should not be in a hurry to place an affected dog on the table. It was always wise to watch the dog in the standing position and whilst moving, because such observations could give a good deal of information. When the dog was on the table and ready for examination one should appreciate the great value of digital palpation and manipulation particularly in relationship to the applied anatomy.

This type of examination was of greater value than radiological examination, and the latter should be used simply to confirm a diagnosis which should be fairly well determined before radiography was used.

In connexion with manipulation and examination, the value of short-acting anaesthetics could not be overemphasised. They were simple and safe, providing a good opportunity for detailed examination. In some cases it was valuable to X-ray the dog in the standing position and, although that could be done early in the examination, better pictures were obtained if they were taken whilst the animal was under anaesthesia.

The film they were now going to see was divided into three parts. The first part dealt with the transplantation of the tibial crest for the correction of patella luxation in a six-months-old bull mastiff. The dog was, in fact, owned by a veterinary surgeon who diagnosed the condition about a month before the operation took place during which time the limb had been immobilised in plaster without effect. It was a case of complete patella luxation not recurrent luxation. The second part of the film illustrated a modified Hauser technique, preferable for small dogs in which it was not wise to transplant the crest as a whole. The third part showed arthrotomy in a Gordon Setter revealing a ruptured anterior cruciate ligament.

Transplantation of the tibial crest was primarily for the treatment of the congenital case, in dogs aged from, say, 3 to 10 months.

The film on "Tibial Crest Transplantation" was then shown.

The Openers

Mr. M. Young, in opening the discussion, said that he would first of all like to congratulate the author on an excellent paper. It appeared to be a most comprehensive and practical appraisal of the subject and, what was more, he as a simple clinician could understand it.

He was in some disagreement with the author regarding the condition of luxation of the patella. While agreeing with the author's remarks as they applied to the condition which occurred as a result of trauma, he believed the situation was completely different in those cases which were of congenital origin. Those cases were usually presented for examination when the puppy was about 1 to 3 months of age and was seen to be partially crippled in one or both hind legs. The affected stifle was flexed and the puppy moved in a crouched position. The patella lay medial to the distal end of the femur and was not freely movable, being held rigid by the pull of the quadriceps group of muscles, for those muscle fibres had never been fully extended by normal flexion of the stifle joint.

The trochlea was easy to palpate and there was little evidence of a patella groove. In fact, in a miniature French

Poodle he had recently examined the trochlea was completely convex, with no sign of a lip either medially or laterally. Due to the tension of the shortened quadriceps it was impossible to place the patella on to the trochlea even when the stifle was extended under anaesthesia.

With regard to the surgical correction of the condition, he was quite in agreement with the author regarding the necessity of transplantation of the tibial crest. It was, in his experience, impossible to place the patella on to the trochlea until that had been done. However, in congenital cases, where no patella groove was present, he had always considered it necessary to prepare one. The trochlea was exposed, and using a fine bone saw—or in the very young animal with soft bone a scalpel—a groove was cut in the trochlea, just wide enough to take the patella and deep enough to hold it securely. The patella could be forced into the artificial groove only when the stifle was fully extended, and the joint was then held in extension by the tension of the shortened quadriceps.

The subcutaneous tissues were then carefully drawn together and the skin incision was closed in the usual manner. The limb was placed in a plaster cast for one week only. The skin sutures were then removed and, from that stage onward, movement of the joint was encouraged. The owner was instructed gently to flex and extend the joint, increasing the movement daily. The puppy used the limb normally after about six weeks and at that stage the patella could be felt gliding smoothly on the trochlea.

Regarding the condition in adult dogs and when due to trauma, the author recommended the use of counter irritants or rest in a plaster cast before surgery was resorted to. Mr. Young did not like to use a plaster cast in those cases and much preferred using counter irritants and massage, with limited exercise allowed on a short lead. Once having decided on surgical interference, he agreed with the method of surgical correction which the author described. However, the author stated that in severe cases, in which the upper part of the medial lip of the trochlea was completely broken down, the prognosis was not good. In such cases, he himself would recommend the cutting out of a new patella groove in the trochlea, as he had described earlier, as well as transplantation of the tibial crest.

The author placed the limb in a plaster cast after the operation. For how long was it kept on?

Mr. Young found that osteo-arthritis of the stifle joint occurred very frequently in relatively young dogs which were grossly overweight. He had particularly in mind the heavy type of Boxer. The prognosis must, of course, be poor but he had achieved some good results by the use of injections of sodium aurothiomalate and by attention to diet and weight reduction. There was no evidence to show that his practice of giving vitamin E did any real good but he had the impression it was of advantage.

The author was to be congratulated most especially on his description of a technique for the repair of the anterior cruciate ligament, a method which Mr. Young was looking forward to using in the next suitable case. He had treated one case of severe stifle lameness due to displacement of the lateral sesamoid. The excision of that brought about a complete recovery, and it would be interesting to hear whether any other cases had been recorded.

Mr. K. M. Dyce, who continued the opening of the discussion, said that he wished first to congratulate the author upon the paper and the very excellent film they had seen that afternoon.

When accepting the invitation to take part in the discussion he imagined he would enlarge upon the functional anatomy of the joint, but that was so well covered in the paper that further remarks upon it would be superfluous. Therefore, he would speak briefly upon the radiographic aspect.

Concerning plain radiography there was little to add to the author's remarks except to support the emphasis put on accurate positioning. The possibilities of using contrast arthrography had been briefly referred to, and it was upon that that Mr. Dyce wished to speak. In that technique the joint capsule was distended with a suitable agent whose density contrasted with that of the adjacent soft tissues. In human radiography, where the method was relatively commonplace, the agent usually employed was diodone which provided a positive contrast; some, however, preferred the use of negative agents, generally air, and his own experience had been almost entirely with that. It seemed to possess several advantages: it was cheap and always available, it was non-irritant and gave pictures that were easy to interpret. Furthermore, unlike diodone, it did not obscure small irregularities in the contours of the soft parts.

The technique of injection was straightforward. The site was prepared in the usual way and the needle was passed through a blind approach into the joint cavity. Air was injected to distend the joint cavity, including its several compartments and diverticula.

The structures visualised in the contrast radiograph that were not visible in the plain films included the capsule, the articular cartilage, the intra-articular menisci and the cruciate ligaments. Lesions of all those components might be shown and, in addition, foreign bodies and crack fractures that were not apparent in the plain films might on occasion be demonstrated. The method was principally used to show the menisci and the cruciate ligaments.

The former were best portrayed in the anterior, and especially in oblique views which appeared as relatively dense wedges of tissue interposed between the condyles of the femur and tibia, and tapering towards the centre of the joint. The lateral meniscus was the larger and appeared to better advantage, which was unfortunate as it was the medial which was the more commonly damaged.

Irregularities in outline indicated damage to the meniscus. It was important to note in this connexion that the lateral meniscus, unlike the medial, was not attached along its entire outer border but was separated from the capsule in two places, where the popliteal and extensor tendons intervened. These tendons were surrounded by extensions of the capsule and in these situations air was normally present at the periphery of the meniscus; a similar appearance on the medial side would indicate separation of the meniscus from its attachment.

Demonstration of the cruciate ligaments was less satisfactory. In the anterior view the two cruciates presented a composite shadow since they were twisted around each other. It was possible to separate the two by fixing the femur in the anterior position and rotating the tibia laterally thus causing the ligaments to unwrap, but the shape of the limbs and the need to protect hands hampered this manipulation. The ligaments also appeared in the lateral view, but the density of the femoral condyles made it difficult to trace their outlines with certainty. This was perhaps the only occasion on which the use of a positive contrast agent would give results superior to those obtained with air.

In conclusion, Mr. Dyce emphasised that he was not advocating indiscriminate use of contrast arthrographs, but fully supported the view that the clinical examination was of far greater importance. However, their use might provide valuable additional information when the results of the latter were indecisive.

The General Discussion

Mr. James Roberts (Newmarket): "I wish to congratulate the author and the opener on this paper, and would especially thank the author for having taken the trouble to present some of his subject by cinematography. I would like to ask him if he had ever found it necessary to remove either the screws or the wire after recovery from the two transplantation operations which he described?"

The Replies

Mr. Singleton, in replying to the discussion, said that Mr. Young had brought up some interesting points in connexion with the condition of recurrent patella luxation. He had discussed that matter with him frequently, and could only conclude that, after 10 years or so in canine practice, he had not encountered such severe cases as those which Mr. Young described. If presented with such cases—which presumably occurred mainly in the "toy" breeds—transplantation of the tibial crest was justified, but it was a bold step to gouge through articular cartilage and down into the bone although Mr. Young's results obviously justified this procedure.

The length of time for which cases remained in plaster varied a good deal. Success was achieved in some dogs which simply would not keep a plaster on at all. They were mainly of the smaller breeds. However, every effort should be made to immobilise the limb for at least 3 weeks, and preferably for 6. The duration could be judged by radiological examination and, as soon as it was certain that the graft had taken, the plaster could be removed.

In answer to Mr. Roberts, it was not normally necessary to remove the wire or screw unless a small fistula developed.

As far as the aetiology of the condition was concerned, there was probably a combination of factors involved, including hereditary predisposition. The cases which developed after the dog had reached adult life were interesting as it was rather difficult to understand their occurrence. However, it was usually found that the patella seemed to ride rather high on the trochlea and it could be imagined that if any rotation took place it would be possible for the patella to slip down the medial side of the lip of the trochlea. If that happened once it could, of course, recur persistently.

Colonel Hickman's remarks about building up the trochlea were very interesting and one would like to hear in future how the procedure referred to worked out. It certainly seemed to be sound in design.

Mr. Singleton said he would never operate on a dog in the knowledge that it was going to be used for breeding. In the case of a pet dog one had to try to please the owner and relieve the animal's discomfort as much as possible. He felt that the surgical proceedings were justified in these cases.

Miss Welch had referred to arthritis of the stifle joint. He had administered interarticular injections of cortisone following Miss Joshua's recent remarks at the Central Veterinary Society, with mixed results. It might well be a procedure to be tried early in the course of this condition.

The vast majority of cases involving the anterior cruciate were not complete ruptures, and if they were rested adequately there was every chance that healing would take place. It had been established by Pfab and Paatsama that a completely ruptured ligament would not heal; whereas an almost completely ruptured ligament would invariably do so.

Mr. Young, also in reply, pointed out that in the operation he had described he transplanted the tibial crest as well as made the groove, thus correcting the alignment. Regarding the use of myocrisin for osteoarthritis he had seen good results and thought it was well worth trying. In his experience it gave very good results in about 65 per cent of cases, another 10 per cent showed slight improvement and the rest no improvement whatsoever.

He would add that he practised in the West End and dealt with a lot of tiny "toy" dogs which were not kept for breeding but purely as pets. They were very much beloved and it was up to the veterinarian to satisfy the public. It was justifiable to try to make the lives of those animals rather more reasonable than they were. A large number of the dogs weighed only 3 or 4 lb.

The Training, Management and Employment of Various Categories of Dogs used by the Army

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Introduction

THROUGH the ages the three main uses of animals to man have been to furnish him with clothing, food and transport. Transport has declined most of the three, but there have been ominous changes in food and clothing, too.

Man is gradually turning from organic to inorganic raw materials, from animal-food to plant and synthetic food and from faith to reason. He is slowly allowing that in principle animals are his moral equals and that his right to rule is limited only by his superior power of intelligence: however, his reason determines his actual behaviour.

Before taking on the responsibility of training animals most people are at one time or another worried about the following age-old controversial questions:—

1. Are the psychic characteristics of animals different from man in kind or only in degree?
2. Do animals possess a soul?

In the age of the horse the British Army was certainly divided on the question of whether animals possessed souls or not. The cavalry and artillery if they but knew it were largely supporters of the Leibnizian monad theory (the "ayes") whereas the infantry were more or less Descartesian (the "noes"). If a Gallup poll had been taken in those far-off halcyon days the veterinary services would indubitably have been placed in the "don't know" group, in which we still find them in this modern atomic age.

The horse has lost for ever his former prestige in the military sphere. He is not by nature an aggressive animal and the ancient poets painted an erroneous picture of him. There is very little real regret among horse-lovers that he has been relieved of his combatant military role after some 2,000 years or more of glorious deeds helping man in his internecine campaigns. He is now destined to end his days quietly in a stable. Perhaps this glorious spirit still lives on in *Pegasus*, the symbol of our indomitable parachute troops.

This is not so in the case of the dog, whose importance to the military machine has waxed or waned in each succeeding generation since the dawn of history. At the moment his prestige is high, and he is one of the main reasons for the existence of the Royal Army Veterinary Corps.

The dog has been man's friend and companion since the Stone Age. From every point of view he has "progressed" upwards ever since he was a camp follower of primitive man on his hunting forays. He has the dubious distinction of being the first "wild" animal to be "domesticated."

We must regard domestication as a psychological process of remoulding a species to tolerate man's company, whereas training involves the compulsion or inducement of the individual animal, through the medium of the stimulation of his primary senses, to carry out man's wishes.

History

In ancient times the dog was the beggar's companion. Greek poets held that unmanageable women were descended from female dogs. This stigma remains to this day.

Slowly, by taking part in hunting and by protecting sheep from wild animals, his usefulness was recognised and he came to be greatly honoured.

Very quickly his extraordinary characteristics enabled him to be recognised as an asset to the military machine. These characteristics consisted of fearlessness and aggressiveness coupled with a loyalty which transcended that of man.

As the methods of warfare changed through the ages so did the military use to which they were put.

History in fact is full of stories of the exploits of dogs in the great battles and sieges. The engraved bronzes and marbles of the ancient cities clearly show the types of these military dogs. Indubitably these armies of long, long ago possessed dog units.

Herodotus states that Cyrus collected a large number of mastiff-like dogs for war. These animals were maintained by four towns whose inhabitants paid no other tax than to provide their food.

According to Pliny, the King of the Garamantes returned from exile preceded by a battalion of 200 dogs. Those who were opposed to his return were set upon by these dogs.

The dog's affection for man coupled with his speed, watchfulness, docility, sense of duty, and finally his acuteness of the usual senses made him (and still makes him) an invaluable aid to any army.

During the Middle Ages they were often used covered in armour like a charger. With spiked collars they were indeed formidable against cavalry. Napoleon used them! So did Christopher Columbus, who employed tracker dogs. In more modern times, most of the European powers had war dogs; many ambulance dogs were used and died in the Russo-Japanese war. The big and strong Pyrenean dog was used by the French to carry ammunition.

War dogs played an important role in the Balkan wars, acting as sentries and helping to locate hidden gun posts. In the Abor Expedition in the Himalayas in the early years of this century we used dogs as sound detectors.

It was, however, during the 1914-18 war that dogs really made their mark in the modern army. The

Germans employed over 30,000 Red Cross and messenger dogs alone! There were over 5,000 killed in the French army during the war.

Pack and draught dogs were used by both French and Belgium armies. It is recorded that one section of sledge dogs (Huskies from Canada) took only four days to haul 90 tons of ammunition to a battery marooned in the Vosges Mountains which men, horses and mules had vainly struggled for 14 days to reach. Jeeps or helicopters may be able to do this nowadays but it is doubtful, especially with modern "priorities" looming so largely at base!

Seas of mud were normal in France in the Great War: messenger dogs could navigate it easily whilst men, mules and horses were bogged down (as jeeps, mules and horses were in Italy during the 1939-45 war). Signal wire was also not immune!

During the 1939-45 war the Germans were the most efficient users of war dogs; the reason simply being, of course, that they had prepared during the inter-war years. Many an Allied agent dropped by parachute in enemy or enemy-occupied territory was captured by being tracked down by trained war dogs.

Russia trained over 50,000 normal war dogs during the war. She also used "Tank Bursting Dogs." These dogs were trained to carry H.E. on their backs which was detonated by an antenna when the dog ran under the indicated tank.

The U.S.A. trained over 20,000 dogs between 1941 and 1943; sledge, pack and infantry patrol dogs were the main commitment. The patrol dog was particularly useful in the Pacific jungle theatre.

The British Army did nothing about dogs between the wars and it was not until 1942 that a war dog training school was formed. Many thousands of dogs were used subsequently, especially guard and mine dogs.

After the war it was quickly appreciated that dogs had come to stay and would, in future, become an integral part of the military organisation. The Royal Military Police were initially in charge of war dogs, but it was quickly and sensibly appreciated that the only Corps in the modern army which was exclusively qualified to cope with the supply, care, training and veterinary requirements of animals was the Royal Army Veterinary Corps.

Consequently the Royal Army Veterinary Corps have for a number of years in every way been responsible for war dogs in the British Army.

Breed, Categories and Employment

In the Army many breeds of dogs are used. The Alsatian is the commonest type, but Labradors, Boxers and Doberman Pinschers are employed. Some exotic breeds have been tried out, including Australian Blue Heelers, Bloodhounds, Mastiffs and so on, but by and large the Alsatian still holds sway as the most popular all-purpose army dog. Regardless of breed, however, there are certain characteristics which should be evident in all dogs selected for military purposes. Physical fitness is, of course, essential, but in addition they must be good specimens of their breed with good conformation. Alertness, energy, stamina and vigour should be evident with a willingness to be taught and a capacity to learn.

Only male dogs over 12 months and under three years are selected for training.

Dogs are obtained for the Army usually either as gifts or by purchase. Occasionally suitable dogs come from dogs' homes and a few are bred. Breeding is not popular in the Army because the period between birth and 12 to 18 months when they are put into training is fraught by so many diseases and nutritional hurdles. It is more economical in every sense to buy a one- to three-year-old dog, which has successfully survived the distemper complex, and has been approved after the usual probationary period of 14 days at the War Dog Training School at Melton Mowbray. During this probationary period the dogs are protected by a dose of "Gamahtine," while their potentialities are assessed.

This initial screening process is very important and is based (perhaps unknowingly by the trainer) on the psychological and physical traits of the dog. Observations are made throughout the training-life of the dog so that the inherent weaknesses or potentialities may be appreciated. If these are obvious then later reclassification or even rejection may be necessary. By and large, however, the initial assessment, if based on a proper knowledge of each type of war dog used in the Army, is usually right.

There are in fact eight categories of dogs used in the Army. *Guard dogs* are the main type of army dogs used in the United Kingdom and are also found in every theatre of the world. They are grouped into Army Guard Dog Units, R.A.V.C., and are used to give greater security to guarded premises and various types of military installations, such as ammunition depots, petrol depots, aerodromes, and so on. These dogs are popular for another potent reason: they reduce very considerably the number of personnel required for guard duties.

The most highly specialised category is the *Tracking Dog*, which has been so successfully employed against Communist terrorists in Malaya, Mau Mau in Kenya, Eoka in Cyprus and in assisting the police in this country. These dogs are trained to follow human scent over any normal terrain.

Other types of dogs used in the Army include *infantry patrol* dogs which alert the presence of any "foreign body" in the vicinity, *Red Cross or casualty detection dogs, messenger or liaison dogs, pack dogs, arms recovery dogs* and *mine dogs*.

Registration

All dogs which are selected for military service are very carefully documented at the War Dog Training School so that they may be readily identified and a complete record of their movements maintained. Each dog is given a *number*, which is tattooed on the inside of the left ear. The Preston system of numbering is used: starting at letter A, the first number in the series is A000, the second A001 and so on up to A999 which completes the first thousand. The second thousand starts from 0A00 to 9A99. The third

thousand will commence at 00A0 and finish at 99A9 and the fourth thousand at 000A to 999A. Thus the alphabet and three numbers provide us with 104,000 possible numbers.

Other means of identification include *name* and full *description*, which are entered up in a master ledger and on specially printed record cards. Finally, there is a veterinary history sheet, which accompanies the dog on his postings the world over and includes a full description plus a complete history of his ailments, illnesses, inoculations and so on. A record of his training and employment is also meticulously maintained.

Equipment and Rations

Each dog in the Army is "on the strength" as much as any man is. The dog-soldier, too, is entitled to an authorised scale of equipment and food.

Each dog is entitled to a collar, lead, tethering chain, kennel, feed bowl, water bowl, dandy brush, comb, and coat in cold weather. His training equipment varies according to his function.

As for rations, each dog is entitled to 24 oz. meat, 16 oz. biscuits and 4 oz. of vegetables daily. (The R.A.F., as a matter of interest, give their dogs 40 oz. of meat a day.)

General Management

Fit and contented dogs respond to training much more readily than ill-managed ones. The aim in all Army dog units is to achieve this objective. Sickness will be reduced to a minimum where the kennel management is good. With dogs, as with horses, a daily grooming is very necessary all the year round. The eyes, ears, teeth, nails and anal glands are regularly inspected. Regular daily exercise, which depends upon the work which the dog is doing, is absolutely essential to prevent obesity, skin disorders and constipation. The exercise is usually organised in squads, and includes long road walks to harden the feet and accustom them to traffic. It is during these walks that the dog learns to walk properly at heel and to ignore extraneous interests. A trained guard dog doing night patrols will only require a little exercise to give it an opportunity of emptying its bowels, whereas a dog kept chained without a run will require considerably more exercise. The exercise must be correlated with the feeding, which must be balanced and adequate for the work being done. The full ration of 1½ lb. fresh, boneless meat, ½ to 1 lb. biscuits and ¼ lb. vegetables is, in my opinion, absolutely essential if army dogs are to be maintained in fighting condition. Tinned meat of any description can replace fresh meat, but not for more than a fortnight out of every month. If tinned meat is fed continuously for more than three to six months, signs of deficiency disease are liable to show themselves, especially amongst dogs living under tropical conditions. Biscuits, too, are very necessary if a dog is to maintain its condition: they are fed mixed with the meat, as is the vegetable ration which furnishes vitamins, minerals and bulk. Although bones are absolutely unnecessary to the health of a grown dog I firmly believe that an occasional big bone tends to boost his morale!

The following feeding rules are usually observed in army dog units:—

1. One meal a day.
2. Hour of feeding the same daily.
3. Never fed just before work or immediately after exercise.
4. Food prepared as near feeding time as possible.
5. Dogs allowed to consume their food undisturbed.
6. Feed bowls removed immediately after feeding except in exceptional cases of shy feeders.
7. Changes of diet brought on gradually.
8. Water allowed *ad libitum*.

Kennelling

Kennels are to be found either as permanent multiple units or as single portable kennels. They all conform, however, in being large enough, watertight, wind- and draught-proof. Kennels are cleaned thoroughly daily first thing in the morning for the dictum "a dirty kennel makes a dirty dog" is indeed true. It is important not to keep the kennel floors continuously wet, and the ground around individual kennels should be regularly raked. Although any kind of artificial heating is quite unnecessary, bedding is usually provided in the form of wheat straw, and rugs are obtainable if necessary.

In large dog units there are separate kennels for isolation purposes and in the canine veterinary hospital. In dog training schools there is also a quarantine section, where newly purchased dogs etc. are kept for at least 14 days.

In tropical countries some special conditions obtain, such as ensuring that kennels are cool and well ventilated, and give protection from sun and rain. In addition, exercise must be carefully supervised; bedding and clothing are not needed, and the advisability of clipping long-coated dogs must be considered.

I found that a permanent dip-bath, using gammexane, was an absolute boon in controlling ticks. The bath was at the entrance to the unit, and the dogs would jump in every day either going out or coming in. This was infinitely better than the text-book method of dipping once a week.

Diseases and Ailments

The dog soldier suffers from the same kind of diseases and ailments as his civilian counterpart.

Military veterinary medicine as a separate specialised entity does not exist nowadays: the fact that dogs are serving in every corner of the world implies that they suffer from local diseases: in the Far East, Heart Worm (Filariasis) and skin diseases are very common, in the temperate zones the distemper complex complicates matters and over-all in both East and West we have the Leptospirosis background.

In every theatre there are modern canine hospitals and pharmacies equipped with the best apparatus including X-ray sets, ultra-therm apparatus and so

on. They are supplied with the most up-to-date drugs and dressings from the R.A.V.C. School and Stores, Aldershot; thus ensuring that the Army Dog wherever he may be serving is covered by an adequate veterinary service.

Training

General

The dog's affection for man is transcendent and inexplicable, and one of our most potent training weapons. However, Schiller's precept that ". . . the animal-machine is kept going by hunger and love" has not been forgotten, especially in certain conditions of environment.

There are no tricks or "gimmicks" to dog-training, which is based solely upon patience, repetition and some knowledge of dog-psychology. There are two basic principles, however, which are adhered to more easily in some countries such as Germany than in others such as the United Kingdom; firstly, that the trainer must be master in every sense, and secondly, that he must be aware of the dog's potentialities and limitations. By and large, the people of these islands are poor dog trainers because of their zealous anthropomorphic views. Whereas in Central Europe every village and town can produce at least one really first-class trainer we can only number a handful of real experts in the whole country.

Most animals are willing to work for a tangible reward (such as food) or punishment (such as an electric shock or pain). The dog, however, is unique: he will work for a caress. Once this intangible affection of a dog is won by his master he becomes a most willing trainee.

Although concrete punishment and reward may have to be used on occasions the greatest success depends upon the eagerness of the dog to serve. The great thing for the trainer is to be able to recognise this quality of willingness in the dog, and to exploit it.

The two essential qualities looked for in Army trainers are firstly, a sympathy and liking for dogs and secondly, absolute dependability. A dog cannot tell how he is being treated, nor can he make a report. Failure on the part of the trainer-handler to look after the welfare of his charge in every sense will mean failure in his training.

Basic Training

Training of dogs in the Army is divided roughly into two phases. In the first there is a basic training period of two to four weeks, which serves to develop a disciplined behaviour essential to more specialised training for specific military functions. In civilian circles this period is called obedience training. In the Army, however, there is no place whatsoever for obedience as an end in itself. Every army dog must be completely obedient if he is to become an efficient member of one of the eight categories of dogs already listed. If basic obedience training has been properly carried out the trainer will know which type his dog is best suited to become, and the second phase (of specialised training) will commence on a happy rational note.

The initial training requires great care, and the trainer must be in complete command all the time. The behaviour, response and efficiency of the finished dog depends upon the care and sensitivity with which the basic training is carried out. Vehicle travel, battle inoculations, jumping, parachuting, helicopter travel, and so on are included as specialised parts of basic obedience training as required. Essentially during this period the dog is taught to obey five basic words of command: Heel, Sit, Down, Stay and Come.

Gestures replace vocal commands as training proceeds.

The gaining of the dog's affection by the handler is of vital importance: if it is not obtained it gradually turns to hostility, and the last state is worse than the first. The dog's training proceeds along lines so that he "grows up" in his training just as he does in body. Each stage is built up thoroughly so that it becomes instinctive, and an invisible link is built up between trainer and dog. The lead, which is this link to begin with, is gradually replaced by confidence and affection.

At all times good work is praised, misunderstandings humoured and disobedience checked immediately. Once the rudiments of each lesson are mastered constant "recaps" are introduced: the dog's interest is never allowed to flag by prolonging a lesson to boredom. Nagging, *i.e.*, continually checking, is as dangerous in dog training as it is unwise in human relations.

Specialised Training

Unlike the Metropolitan Police (who train their dogs to be trackers, patrol, guard and messenger all rolled into one) the Army sticks to the fundamental principle that, owing to the dog's natural limitations, to train him to do more than one specialised job is to diminish the best contribution he can make. Consequently, his basic traits are emphasised during his specialised training, and by a process of experience and association of ideas the stage is reached whereby the soldier comes to rely on the dog to accomplish certain specific things (such as act as a guard or track, etc.) which he cannot do as well or as quickly himself. Whereas in basic training the dog relies on his handler, in specialised training the handler must come to depend on his dog.

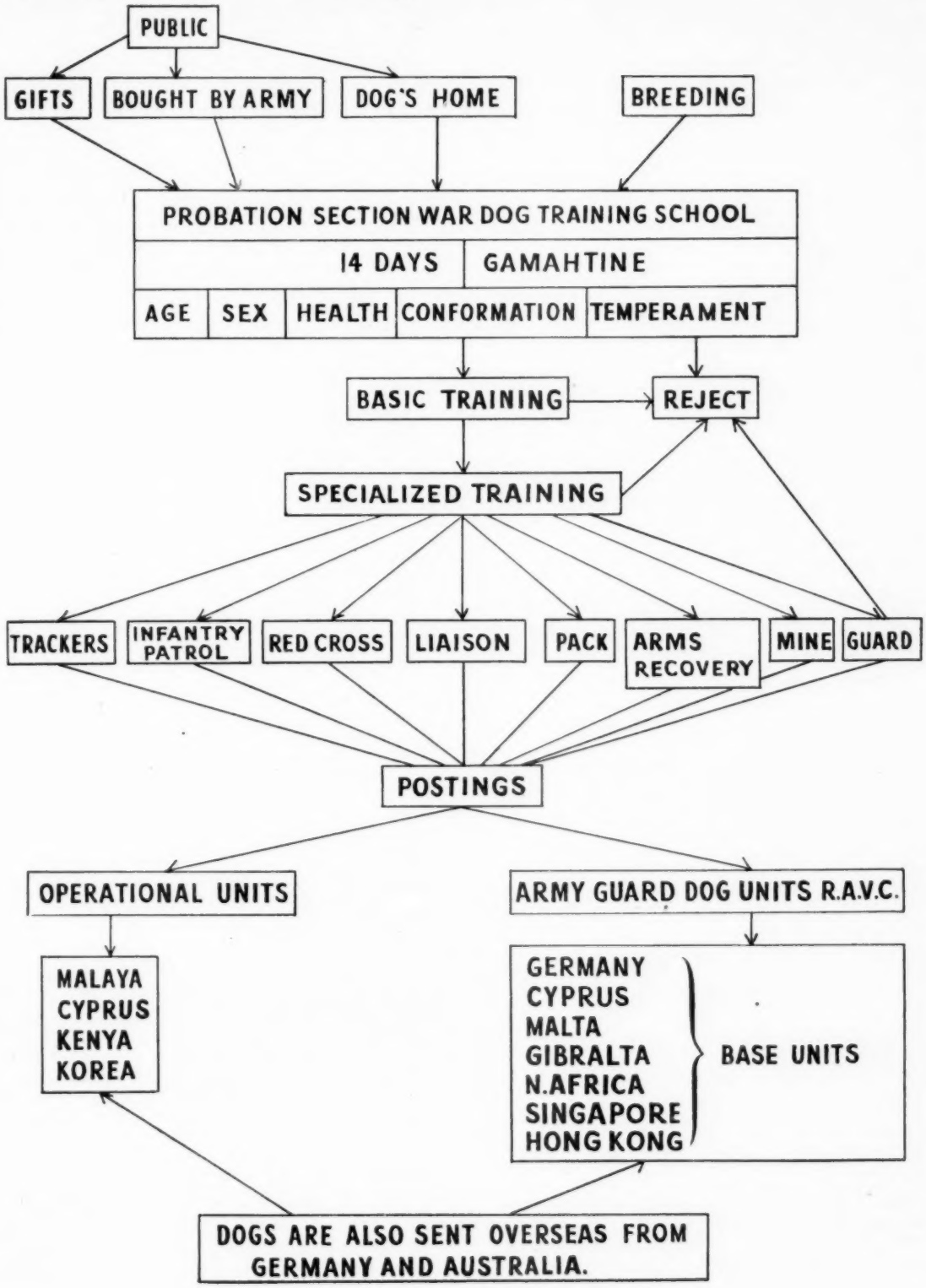
The detailed specialised training of some of the different types of army dogs is given in the training appendix.

Summary

The Royal Army Veterinary Corps have, for a number of years, been responsible for the supply, training, care and veterinary requirements of war dogs in the British Army.

The part which the dog has played in the military sphere since the dawn of history to the present day is briefly outlined.

A description is given of the different breeds and the various functions of the eight types of dogs used in the Army. These include guard dogs,


PUBLIC
GIFTS
BOUGHT BY ARMY
DOG'S HOME
BREEDING
PROBATION SECTION WAR DOG TRAINING SCHOOL
14 DAYS
GAMAHTINE
AGE
SEX
HEALTH
CONFORMATION
TEMPERAMENT
BASIC TRAINING
REJECT
SPECIALIZED TRAINING
TRACKERS
INFANTRY PATROL
RED CROSS
LIAISON
PACK
ARMS RECOVERY
MINE
GUARD
POSTINGS
OPERATIONAL UNITS
ARMY GUARD DOG UNITS R.A.V.C.
MALAYA
CYPRUS
KENYA
KOREA
GERMANY
CYPRUS
MALTA
GIBRALTA
N.AFRICA
SINGAPORE
HONG KONG
BASE UNITS
DOGS ARE ALSO SENT OVERSEAS FROM GERMANY AND AUSTRALIA.

trackers, infantry patrol, Red Cross, messenger, pack, arms recovery and mine dogs. The method of selection of dogs and of their registration is outlined, and their general management in temperate and tropical theatres discussed. Diseases and ailments are mentioned very briefly whilst training and employment is described in detail from the theoretical and practical angle.

APPENDIX

Training of Army Dogs

Basic Training

The dog is taught to obey five basic words of command. The same word is *always* used for the position the handler wishes the dog to assume. The actual word is of little importance, but it must be crisp and easy to say. So as to gain the dog's attention the word of command should be preceded by the name of the dog, *e.g.*, HITLER—COME.

Commands need not be given in a loud voice but emphasis is needed on the tone. These *commands* must be instantly obeyed: there is no question of a request being complied with!

1. *Walking at Heel*

At the command "HEEL" the dog should walk on a loose lead at the left side of the trainer with his shoulder opposite and level with the trainer's knee.

Method

(a) The handler retains the lead in his right hand, lengthening or shortening it as necessary.

(b) He walks forward at a normal pace, *at the same time* saying ". . . Name of dog . . . HEEL." The dog will recognise his name and be alert but at first "heel" will be meaningless to him.

(c) Any reluctance to follow must be countered by smartly tightening the lead with words of encouragement and repetition of the dog's name and command. Once the dog follows willingly the correct position as above must be assumed.

(d) Checking is done by a sharp tug and NOT by a long even pull.

(e) The slack lead must NOT swing in front of the dog's nose.

(f) As training progresses turns etc. are introduced.

(g) Time for practise—15 minutes two or three times daily for first three or four days.

(h) It is always useful to have a long, narrow alley for awkward dogs.

2. *Sitting*

On the word of command "SIT" the dog must have only his hindquarters and paws of the front feet on the ground. He should never be left for any length of time in the sitting position. Where it is intended to do so he should be put in the "Down" position.

Method

From Standing Position

(a) The lead is held in right hand only. Left hand is placed on hindquarters and pressed down firmly *at the same time* giving the command "SIT."

(b) Each time dog rises (a) is repeated.

(c) When dog sits temporarily, straighten up slowly, keeping left hand under muzzle.

(d) Encourage as necessary.

From Down Position

(a) Left hand placed on hindquarters.

(b) Forequarters raised by lifting with lead *at the same time* giving the command "SIT."

(c) Encourage as necessary.

When moving forward the command "HEEL" is given.

3. *Down*

On the command "DOWN" the dog must place both fore and hindquarters on the ground with the forelegs extended in front. He must lie, whether standing or sitting.

Method

(a) The handler grasps lead near collar, gives the command "DOWN" and *at the same time* makes dog lie down with a series of downward jerks.

(b) If dog refuses the forelegs are grasped and pulled forward. The command "DOWN" is given *at the same time* and the lead is pulled down as well.

4. *Stay*

On the command "STAY" the dog should remain in the position he was in when the command was given. It is usual to give this command in the "DOWN" position, although it may be given in the standing or sitting positions.

Method

(a) The command "STAY" is given and handler gradually backs away to the fullest extent of the lead pointing one forefinger at the dog.

(b) Progressively repeat until handler can walk away out of sight without dog moving.

5. *Come*

The command "COME" is given from the Stay position and is always preceded by the dog's name. The dog returns immediately to his trainer, sits in front of him, and on the command "Heel" walks around behind the trainer to his left side and sits. This is the most useful part of obedience training, and can be used on many occasions. It teaches the dog to approach the handler with head up and tail wagging; not cringing.

Method

(a) Handler gives commands DOWN and STAY and backs to the fullest extent of the lead and faces the dog.

(b) Calls dog ". . . Name . . . COME."

(c) When dog comes he is made to SIT facing the handler.

(d) The command HEEL is then given and he transfers the lead to his left hand and brings dog to the heel position where it is given the command SIT.

Off the Lead

Thoroughness of previous training on the lead and the tone of voice, helped by the dog's affection and willingness, will determine how the dog behaves off the lead. The transition from working on the lead to that of working off the lead should be very gradual, and will depend on the trainer insisting *at all times* on compliance of ALL his commands immediately.

Jumping

Jumping should not begin until the dog understands and responds to all the basic commands.

Small hurdles 1 foot high should be used initially. The handler with dog at heel approaches the hurdle, steps over, and then encourages the dog to jump. As the hurdle is approached the command UP should be given. The height of the hurdles should be gradually increased.

The aim in mind is to make the dog confident of jumping or scaling all kinds of obstacles.

Battle Inoculation and training a dog to become accustomed to battle noises is important. A gun-shy dog is quite unsuitable for Army purposes.

Vehicle Travel training is also carried out. *All* army dogs must be able to travel in wheeled and tracked vehicles over the roughest country without being nervous or sick.

Aeroplane and Helicopter Travel: most dogs will travel in helicopters and aeroplanes without much fuss. This has been the accumulated experience in Malaya, Kenya and Cyprus.

Parachuting

Continuous and progressive training of courageous, energetic and willing dogs has produced efficient parachute-dogs. There is never any fear or distress either when loaded in the aircraft or on arrival on the ground. The parachute is opened by the normal static line with automatic quick-release fitting.

Specialised Training

GUARD DOGS are normally used for the protection of vulnerable points such as ammunition depots.

Temperament: Only dogs which are naturally aggressive are chosen. Nervous or gun-shy dogs can never become good guard dogs.

Breeds: Usually Alsatians are used, but Boxers, Rottweilers, Doberman Pinschers and other dogs weighing between 60 and 80 lb. are suitable.

Standard Required: A trained guard dog must:—

1. Be obedient to the basic words of command plus the commands ATTACK and LEAVE.
2. Be able to alert his handler when anyone approaches by straining on the lead.
3. Be able to point in the direction of hidden persons.
4. Attack and hold a man when ordered.
5. "Leave" when ordered.

Method

(a) *Static Sentry. Stage I:* The dog is taken to a wooded area. A baiter with a switch lies hidden. He approaches the dog, which is sitting by his handler's side, in a stealthy, suspicious manner. As soon as the dog becomes aware of the baiter's presence the handler encourages him by saying, "GOOD DOG. WATCH HIM."

The baiter annoys the dog by switching at the dog's legs, and he becomes resentful and attacks. The handler encourages the dog by patting him.

After 10 to 15 seconds the baiter runs away and the handler gives the command "ATTACK" and gives chase with the dog for 20 to 25 yards. The baiter disappears amongst the trees and the dog is praised effusively. The dog *always wins.*

Stage II: The dog is now taught to attack and leave a padded sleeve. The same procedure as Stage I is adopted, but the baiter has one arm completely protected by a padded sleeve.

When he gets within 3 to 5 yards of the dog the trainer gives the command "ATTACK" and moves forward sharply. The dog is encouraged to attack and worry the padded arm, and at the same time the switch is used on his legs. After about 15 seconds the baiter stands motionless and the trainer gives the command "LEAVE." If the dog refuses the trainer forces him to do so. The baiter now retreats rapidly and again the command "ATTACK" is given, running with the dog until the baiter disappears from sight.

Stage III: As the dog progresses, the baiter drops the padded sleeve and runs away. The dog must leave the sleeve and give chase with the trainer. This prevents the dog becoming sleeve-conscious.

The dog is always praised after each episode.

(b) *Patrolling Sentry. Stage IV:* When the dog has become proficient at static sentry work he is taught to detect a person in hiding and, if ordered, to attack him. This is done at first on the lead and with the baiter's arm protected by a special sleeve. Later he is allowed to attack, off the lead, a baiter completely protected by a padded suit.

Stage V: Finally the dog is fitted with a strong muzzle and ordered to attack a baiter wearing no protective clothing.

Period of training is six to eight weeks.

RED CROSS OR CASUALTY DETECTION

The type required is a medium-sized intelligent under-aggressive dog with a good nose. Labradors and Collies are most commonly used.

The trained dog must be obedient to the basic words of command plus "SEEK" and be able to range over a given area, and on detecting a casualty return to his handler and sit. He must then lead his handler to the casualty.

Period of training: four months.

INFANTRY PATROL

The intelligent, fairly aggressive type is the best to train as an infantry patrol dog. When trained he must give silent warning of the presence of an individual or group in a patrolled area. Points up to 500 yards are possible under favourable conditions. The Alsatian has proved the most useful breed.

The patrol dog works by "air scent" and hearing, and is very useful in giving silent warning of ambushes, attempts at infiltration and the presence of any "foreign body" before such presence can be detected by a human. He can be employed either on a lead or loose in front of a patrol. When moving to an operational area the dog is kept at HEEL: while in this position he knows he is OFF DUTY. When ON DUTY the collar is removed and either the pilot rope is put on and the dog commanded to SEEK, or the dog works loose and the command SEEK is given.

The dog points by one or a combination of the following signs:—

(a) Raising of head and pricking of ears.
(b) Tensing of body.
(c) Tail wagging.
(d) Keenness to investigate.

The ability of the handler to "read" his dog determines the efficiency of the team of handler and dog on patrol.

TRACKING DOGS

Only dogs with good noses are selected for training. Excitable or nervous dogs are not suitable and aggressiveness is not important. Intelligence, willingness and power of endurance should accompany the good nose if possible. Labradors and Alsatians are the usual breeds chosen: the classic tracking dog —the Blood Hound—is seldom used in the Army.

A trained tracking dog should be capable of following the track of a human scent up to a few days' old. The prevailing weather conditions, of course, will have a direct effect on his efficiency.

Method

In the early stages of training only virgin, open grassland is used.

Stage I: The dog is initially trained to get his nose down and to locate his own trainer. When this is successfully accomplished the dog is rewarded with a piece of meat. The length of track is gradually increased as training progresses.

The track is laid down-wind so that the dog cannot wind the quarry and has to rely on his nose. The trainer drops his handkerchief, moves down-wind to a distance of 20 yards. A second trainer removes the collar and lead and puts on the breast harness and rope. The dog is then allowed to smell the handkerchief, given the command "SEEK" and encouraged to track. If necessary the trainer in hiding will shout or whistle to attract the dog's attention.

Stage II: When the dog can complete tracks of 50 yards a stranger is used as a quarry in all future training.

The length of tracks, which are still straight, and the time interval are gradually increased. If, during a track, the dog becomes uncertain, he is allowed to smell the handkerchief or other article.

Stage III: The track should be now up to 150 to 200 yards. A right angle is introduced. The type of ground is varied and the time interval increased up to one hour.

Stage IV: The length of the track is increased up 1 mile and more turns are introduced.

Stage V: The dog is required to pick out the quarry at the end of the track by picking him out in an "identification parade."

Stage VI: Cross tracks are introduced.

Stage VII: More difficult working conditions are introduced, *e.g.*, across streams, roads, near built-up areas and so on. He is tried in all kinds of weather.

General. The training is carried out thoroughly and slowly. It is essential that the dog has a percentage of successful tracks, *i.e.*, finding his quarry, otherwise he may become disheartened. An occasional simple training track to restore confidence may be necessary.

Period of training: about one and a half to two years.

Special Technique Used in Training of Tracking Dogs in Malaya, 1952-4

Period of Training—Three Months

Method: The dog is prepared by the reduction of food so as to create an incentive through the hunger reflex.

Stage I: The dog is taken to the training area (slightly overgrown rubber) with lead on collar. The track layer carries an open tin of meat and a meat drag and proceeds to tease the dog with the meat until the dog becomes keen. The track layer backs away a short way, drops a piece of meat and the drag and walks some 50 yards, dropping small meat squares on the route to a place of hiding.

The handler must encourage the dog to watch the track layer and allows the dog to search forward to the first piece of meat. At this point the lead is transferred to the harness and the dog encouraged to "SEEK."

At the end of the track the dog is petted by the track layer and given a portion of the feed. The process is repeated three to four times each day.

Progressively the distance is increased to 200 yards without increasing coldness of track and with a gradually diminishing amount of teasing.

Stage II: Intermittent drag with meat.

The handler takes the dog to the start of the track by a *different* route from that taken by the track layer. The dog finds the first piece of meat, the lead is transferred to the harness and the dog given "SEEK" and then every encouragement. On completion, the dog is petted by the track layer and fed.

Progressively in this stage the distance is increased to a maximum of 440 yards and the drag positions and frequency are varied. At the end of the stage the dog should competently follow a track of drags and dropped meat with the dog's rations in a *sealed tin.*

Stage III: The meat on the track and the amount of drag is *gradually* reduced until only the first piece of meat remains at the track commencement.

Stage IV: In this stage the piece of meat at the track commencement is gradually moved towards the end of the track.

Stage V: Time is gradually increased so that the track is two to four hours' cold.

Stage VI: In this stage time, distance, terrain, are varied so that the dog for issue purposes will successfully complete a track two hours cold two miles long. Additionally before issue, a dog should have completed successfully an overnight track. During training dogs are acclimatised to swamp; being carried on the shoulders; swimming; and so on.

ARMY WAR DOGS

Category	Breed	Employment	Training
1. Tracker	Alsatians Labradors	Work by " ground " scent and trained to follow the trail of a human being. Now being employed in Malaya and Cyprus on operations. A great factor in helping to beat the Mau Mau in Kenya 1953 to 1956.	Only dogs with " good noses " are selected. The training is sure and thorough, taking up to two years, and proceeds slowly from finding his own trainer through six or seven stages to complicated tracks over difficult country.
1a. Direction-finding Trackers	Alsatians Labradors	In Malaya against Communist Terrorists	In Malaya in 1952–4, owing to the urgent call for tracker dogs, the training period was cut down to three months using a special technique.
2. Infantry Patrol	Alsatians	Work by " air scent " and hearing and are trained to give silent warning of any individual or group by pointing. Gives silent warning of ambushes and infiltration. In the early days in Malaya when CTs were plentiful, used extensively. Also employed in Germany, Korea and other theatres.	Pointing at the " enemy " is indicated by pricking of ears, tailwagging, etc. Barking is discouraged. The trainer must " read " his own dog. Period of training three months.
3. Red Cross (Casualty Detection)	Labradors	Trained and used to aid R.A.M.C. in locating wounded on battlefields and other areas such as in bomb debris, hideouts, etc. The dog " reports " his discovery and leads help to the casualty.	The collar always has a Red Cross insignia. The training covers searching, reporting and leading. Eventually he understands that all three make up a single entity. Period of training four months.
4. Messenger (Liaison)	Alsatians	Trained to carry messages up to one to two miles at great speed. Can also carry a few supplies and lay signal wire. In wireless failure will establish communication.	Two trainers divide the dog's affection and interest between them by feeding and exercising the dog in turn. The training subsequently is based on the dog's affection for his two trainers. Period of training three months.
5. Pack	Alsatians Danes Boxers, etc.	Carrying supplies, ammunition and medical equipment.	Combination of messenger dog training and specialised pack load carrying. Period of training three months.
6. Guard	Alsatians Boxers Doberman-Pinschers	Guarding military installations, such as depots. Increases the efficiency of guards and has a potent deterrent effect against would-be trespassers. Reduces manpower. Mainly employed at night.	Trained to give warning to handler by growling, barking or a silent alert. Normally worked on a lead. Occasionally they are worked loose in a confined area. The dog must learn that his handler is the ONLY one to be trusted. Period of training one to two months.
7. Mine Detecting	Labradors Mongrels	Assistance to Royal Engineers in clearing mine fields especially when non-metallic mines are used.	The Reward System of training is used. (The U.S. Army use the Fear or Repulsion System of Training). Period of training four months.
8. Arms Recovery (Cache)	Labradors Mongrels	Trained to detect caches of arms buried to depths beyond the range of electrical mine detectors. Used in Palestine, Malaya, Cyprus, etc.	As for mine dogs.

THE SPEAKER'S INTRODUCTION

Major Wilkins said that it gave him great pleasure when he was asked at the beginning of the year to prepare a paper on army dogs. He felt keenly the honour of addressing the Congress.

At the present stage of the Congress, after a whole week of unbridled debauchery (both scientific and physical) it was quite natural for very little of the spoken word to penetrate farther than the external auditory meatus. Furthermore, it must be assumed that not more than 50 per cent. of those present had read the paper. It was his intention, therefore, to summarise what had been written and to expand one or two of the more interesting points.

They all knew that verbalism was the vice of scientific literature—the gobbledygook of the scientist beat that of the civil servant hollow. Luckily, the subject of army dogs could not be classed as scientific in the usual sense of the word and so he could not be accused of that vice. In fact, on reading the paper for the second time the previous week he was struck by its simplicity! He was struck also by an omission which he wanted to rectify now. In addition to his own experience, he used the army manual *Training of War Dogs* 1952 in writing the paper and dipped into that extraordinarily interesting book *Animals, Men and Myths* by **Morus.**

In the paper he had tried to sketch an outline of what the army dog did and the fundamental principles of its training. Quite a bit of padding was put in concerning the part which dogs had played in the military sphere through the ages and details of some controversial training procedures. No doubt many of them were at the moment burning the seats of their chairs and simply waiting for him and the eminent opener of the discussion to finish, before jumping up to slay him and thereby provide a lively discussion. *Morituri te salutamus.*

He was prepared to ward off, with the sword if necessary, fanatical obedience show fans who were rigidly bound by the ring judges; and to plead ignorance and military security when perhaps unable to answer questions that were raised.

The following was an extract from Sir Frederick Smith's book *The History of the R.A.V.C.* 1796-1918, page 188:—

"The question of the employment of dogs in our army was first introduced by an officer of the veterinary department—Vet. Lt.-Col. E. E. Bennett, in March, 1889. . . . In all that has subsequently been published on this question and on the practical value of dogs in the late war (1914-18), I have never seen it stated that the subject was first introduced and demonstrated by an officer of the Army Veterinary Department."

Another pioneer of war dog practice in Great Britain was the late Lt.-Col. E. H. Richardson, Sherwood Foresters. Col. Richardson had always been a believer in military dogs.

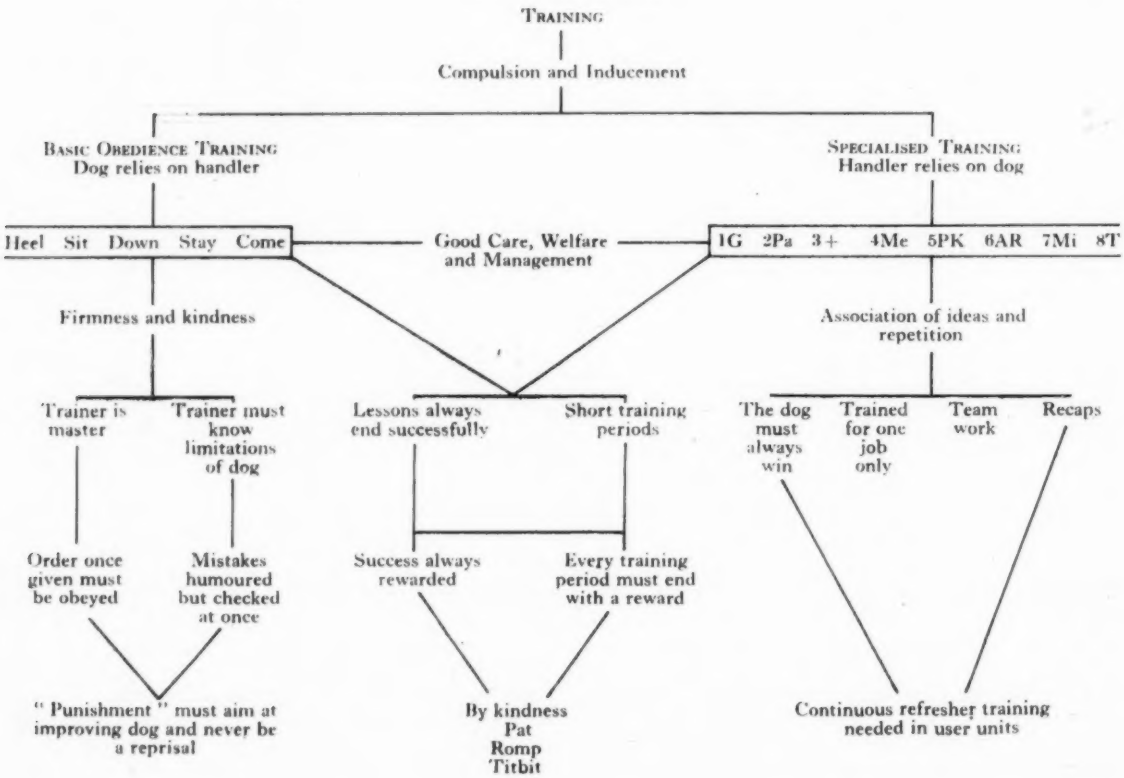
Long before the Great War, and continuously up to the outbreak of hostilities in 1914, he urged the use of dogs by the British Army, but failed to convince the War Office. When hostilities broke out in 1914 Britain had one Airedale (killed later in the Aisne with the 2nd Norfolks); whereas Germany, at an order signed by Ludendorf, mobilised nearly 10,000 canine warriors.

It was due to officers at the front writing to Richardson requesting trained dogs, which he supplied from his private kennels, and the remarkable exploits of those dogs at Vimy Ridge, that the attention of the War Office was eventually attracted. The upshot was the establishment of the war dog school at Shoeburyness, with Richardson, promoted Lt.-Col., as Commandant.

After the Great War, until 1942, nothing more was done about employing war dogs in the British Army.

Incidentally, Col. Richardson was also the pioneer of the use of dogs in the police force in the United Kingdom.

ARMY WAR DOGS


TRAINING
Compulsion and Inducement
BASIC OBEDIENCE TRAINING
Dog relies on handler
SPECIALISED TRAINING
Handler relies on dog
Heel Sit Down Stay Come
Good Care, Welfare and Management
1G 2Pa 3+ 4Me 5PK 6AR 7Mi 8T
Firmness and kindness
Association of ideas and repetition
Trainer is master
Trainer must know limitations of dog
Lessons always end successfully
Short training periods
The dog must always win
Trained for one job only
Team work
Recaps
Order once given must be obeyed
Mistakes humoured but checked at once
Success always rewarded
Every training period must end with a reward
"Punishment" must aim at improving dog and never be a reprisal
By kindness
Pat
Romp
Titbit
Continuous refresher training needed in user units

After years of effort he succeeded in persuading the Berkshire Constabulary to use dogs. Clewer police station Windsor, had the honour of being the first to use police dogs, in 1909.

With regard to training, the real crux of training dogs (or children) was perhaps to know when to reward or correct the dog (or child), irrespective of which side one got out of bed in the morning. Patience and never losing one's temper were the greatest virtues. At all costs, the dog's affection must be won. Misunderstandings should be humoured, good work praised, and disobedience checked immediately. Reprisals should never be resorted to. A dog had no memory as a human being understood it and worked like a child before speech was attained—the baby must be induced not to put its finger in the fire or it must be compelled by force not to do so. In dog training fine anthropomorphic views of discomfort, luxury, promises, honour, good, bad, evil and so on must be put aside.

The following illustrated a simple scheme of training, drawn up rather like the order of battle of an atomic division. Its one virtue was simplicity—it tried to bring order to the intangible and imponderable.

Major Wilkins said he would like to mention briefly some lessons learned in the employment of operational dogs in Malaya against communist terrorists, in Kenya against Mau Mau, and in Cyprus against Eoka.

It had been made abundantly clear that despite the progressive and rapid advancement in mechanisation, dogs trained for various military rôles were an important supporting arm. Operationally, their value had been proved in various post-war colonial police operations. The R.A.V.C. had acquired considerable know-how on methods of training and of operating dogs in a great many climates. That knowledge was quite unique and there was a tie-up on the veterinary side. It was strange to hear that in the new model army, dogs were being handed back to the R.M.P.

Certain general lessons common to all three theatres of operations could be summarised as follows:—

(a) Regular exercise to keep a dog in the peak of physical fitness and stamina was a *sine qua non*, otherwise it became a dangerous liability;

(b) Dog and handler must become a team, improving progressively. The handler must not only be a volunteer but show himself determined and self-reliant;

(c) Continuation of training was vital;

(d) The person employing dogs must have confidence in their ability and a knowledge of their capabilities.

To glance very briefly at three trouble spots, he would turn first of all to Kenya, which had recently returned to normality. Few people outside Kenya itself realised the extent to which the army used dogs in the emergency in East Africa. Reference to two random individual successes might bring the point home.

First Sgt. Rowland, and Bloodsome a Labrador tracker, working with Charlie Company, 7th Btn. Kings African Rifles, were responsible for tracking down and killing 13 Mau Mau terrorists, including the self-styled "Brigadier General Muthumbia," in an action above the 10,000 feet line on Mount Kenya.

Secondly, Private Law and Labrador Benny tracked down and were responsible for the killing of three gangs of Mau Mau.

Such stories could be repeated many times over. Some trainers of dogs in the Army had been considered of such value that they had obtained jobs with local police forces after release. Quite a few were decorated including one R.A.V.C. handler who was awarded the George Medal.

In Malaya tracking and infantry patrol dogs had been successfully employed in jungle operations for the past 5 years. Climatically and geographically Malaya was a very difficult country for dogs. Swamp was no longer an insuperable obstacle for the tracking dog. Infantry patrol dogs worked best when loose in front of the patrol instead of moored to a handler.

Two typical recent reports would give an idea of the usefulness of dogs in Malaya.

First, at 7.15 p.m. on a day recently, four communist terrorists were ambushed near a village. During the engagement one terrorist was wounded but escaped. Tracker dog Lew was introduced to the track at 3.15 a.m. (8 hours later) and followed it for 150 yards to a roadside. It was then decided to call off the follow-up until first light. At 6.30 a.m. Lew was again put to work. He followed the track through rubber and made contact with the terrorist at 7 a.m. Approximately 50 yards from the terrorist the dog pointed, but the handler thought the dog had made a mistake and continued the track. The terrorist was seen at a distance of 7 yards lying in a depression. He was killed but not before he had shot Lew in the face. Lew had since recovered.

Secondly, a patrol of the 1st Btn. Rifle Brigade, acting on information, was making for a communist terrorist camp.

ARMY WAR DOGS

PRINCIPAL VETERINARY CONDITIONS AFFECTING EFFICIENCY

United Kingdom	Germany	Cyprus and Middle East	Kenya	Malaya and Far East
1. Leptospirosis	1. *Infections* (*a*) Leptospiral nephritis (*b*) Distemper	1. Heat exhaustion	1. Tick fever	1. Heartworm
2. Diarrhoea	2. *Skin conditions* (*a*) Eczema (*b*) Mange (*c*) Sebaceous cysts	2. *Skin conditions* (*a*) Eczema (*b*) Mange	2. *Skin conditions*	2. Hookworm
3. *Skin conditions* Pedal eczema Scrotal eczema Sore feet	3. *Surgical* (*a*) Wounds (*b*) Zeps operation for otitis (*c*) Neoplasms	3. Otitis externa (caused mainly by spear grass)	3. Wounds N.B.—Wounds are quick healing	3. Otitis externa
4. Bites and punctured wounds	4. *Miscellaneous* (*a*) Diarrhoea (*b*) Arthritis (*c*) Anal fistulas (*d*) Corneal ulcers	4. Conjunctivitis		4. Sore feet
5. Premature ageing		5. Wounds		5. Wounds N.B.—Wounds are slow healing 6. Maggots

About 10 minutes after starting, Sailor suddenly pointed at right angles to the axis of the patrol. Offensive action was taken and 3 communist terrorists were killed. The range of the point was 45 yards.

Could one doubt the value of dogs to the army after hearing such reports? Certainly Tommy Atkins had come to regard them with respectful affection.

In Cyprus there was a similar tale of successes which had helped in defeating the terrorists. An interesting and important function of mine dogs in Cyprus was their use in discovering arms and ammunition caches. Some of them would "point" at objects hidden in loose stone walls (like those in Cornwall) so long as the object was not much above the head level of the dog.

The deterrent value of guard dogs must run into the saving of hundreds of thousands of pounds of public money annually. When guard dogs and handlers were given a rest on Christmas Day in Singapore a few years ago—it is normally a 365 days duty per year!—a vast amount of stores valued at many thousands of pounds disappeared.

Major Wilkins said he would end with a few words on the veterinary side. He had summarised in a Table the principal conditions which caused wastage amongst army dogs in the different theatres of the world.

The Opener

Captain N. Liakhoff, in opening the discussion, said that the excellent paper by Major Wilkins on the training of dogs for various uses by the army provided much material for interesting discussion. He would like to raise a few points from his own particular outlook and to outline the difference between the training of guide dogs and the training of dogs for any other purpose.

The work of a guide dog differed fundamentally in one psychological aspect from that of any other trained dog. All trained dogs worked in one of three psychological states:—

1. Freedom;
2. Partial freedom: when restricted by a long, supple leash, but still retaining a certain area of individual independence of movement;
3. Captivity: when attached closely and firmly to the master and deprived of any area of individual independence of movement.

The harness, in which it was necessary for the guide dog to work, created the psychological state of captivity by depriving the dog entirely of any area of individual independence of movement That captivity was not resented by or uncomfortable for the dog, but it remained true that it was captivity in the psychological sense. It was therefore necessary in selecting guide dogs to choose those dogs which were temperamentally suited for the particular need, that was to say, dogs which were able to work in captivity without their temperamental traits being adversely affected.

The guide-dog trainer, when assessing a dog's temperament, marked its points and recorded his findings by the use of a special system. A report on a dog by an experienced trainer, set down in that way, was so exact that another experienced trainer would receive from it a complete picture of the dog's temperamental make-up without seeing the dog at all.

In referring to a chart on temperamental traits in the dog, Captain Liakhoff said that nervous dogs were not suitable as guide dogs, nor were those with a high degree of suspicion or "pure aggression." Protective aggression could be adapted if it were not developed too highly. A guide dog required to hear well and to have a high degree of bodily sensitivity. The control of the trainer, and subsequently of a blind person, would be vocal control.

Mr. James Roberts (Newmarket): "I wish to add my congratulations to the author of this paper, and to the opener for his contribution. I would very much like to know whether the olfactory sensitivity of tracking dogs has noticeably diminished after recovery from diseases which involved inflammatory reactions of the nasal mucous membranes."

A number of other points were raised in the discussion, but manuscript was not available from the speakers—Edit.

The Reply

Major Wilkins, in replying to the discussion, said that only male dogs were used in the army. In Cyprus bitches had been very much easier to train and they worked better, but because of the administrative difficulties they were not used. It was, of course, known that a different scent emanated from each human being. The number of scent particles touching the sensory endings of the dog determined its tracking efficiency, and if it had any deficiency of the olfactory senses there would be a marked limitation on its sensing power.

The army dogs were old enough to have had distemper or were apparently not going to have it.

A police dog was trained to be a tracker, a patrol dog and a guard dog, but any dog's natural instinct was to follow another dog and sometimes to fight it. It was not natural for a dog to follow a human scent. Army dogs were trained to follow or to fight human beings and, if so ordered, the obedient dog would not do otherwise. The efficiency of a dog was judged by whether it was likely to go out of control. Dogs were not trained to smell or hear more efficiently. They either had a good nose or they had not.

An attempt had been made to breed dogs which were particularly suitable for work, and by and large it was unsuccesstul. In Malaya an experiment was carried out to breed, from a Boxer and an Alsatian, dogs which had the best characteristics of both, but it was not worth while.

Some soldiers felt that when they left the army the dogs they handled would die of a broken heart. Some of them were prepared to pay a lot of money so that the dogs might return with them to the United Kingdom. In fact, within a week a dog would adapt itself completely to a new master.

Captain Liakhoff, after years of experience, had a vast knowledge of the psychology of dogs. The boundary between a dog's intelligence and instinct was not as distinct and clear-cut as some people imagined it to be. Sensitivity was exceedingly important in a dog that was to be trained. It was important for the dog to be sensitive—not under-sensitive or over-sensitive. A soldier who could orientate himself in a featureless landscape or in impenetrable jungle was rightly considered to be intelligent. Nearly every dog could do that very much better than man could but it was ascribed solely to instinct. If it were kept in mind that animal instinct and human intelligence were, if not exactly the same thing, very much alike, new possibilities of understanding animal behaviour must arise.

It was difficult for a man to appreciate the smelling powers of a dog, which were perhaps 10,000,000 times greater than his own. A dog lived in a world of smells, just as a human being lived in a world of vision. While dogs lived in a world of odours, a few were far more susceptible to them than others. They were the exceptional ones which could follow old ground scents for miles, along tarmac or across snow.

To end on a platitudinous note, man was himself a domesticated animal in an artificial medium created by himself, called "modern civilisation." As they all knew, environment produced alterations in functions, which in turn produced alterations of anatomical structure. Man was certainly less wise and less intelligent now than he was in former centuries; only the "specialists" had more knowledge. Could the present insidious environment make men lose their morality and cause a breakdown of the human mental structure? Should man begin training himself in the ways of nature once more and leave dogs and the so-called backward races in their happy Elysium?